Cronus Pharma Product Catalog

Dedicated to Providing Innovative and Cost-Effective Pharmaceuticals

Cronus Pharma






Table of Contents

Who is **Cronus Pharma?**

Cronus Pharma is a privately held veterinary pharmaceutical company headquartered in East Brunswick, New Jersey, dedicated to providing innovative and cost-effective pharmaceuticals to the animal health market. Our team of seasoned industry professionals have been intimately involved in the establishment and growth of several pharmaceutical manufacturing and distribution firms in both the human and animal health pharmaceutical industries.

Through our in house R&D and acquisitions, Cronus has an extensive product portfolio of over 50 approved products of which 11 are currently marketed serving the companion, equine and food producing animal health markets. We recently built a new FDA registered manufacturing facility located in Hyderabad, India with broad capabilities including solid oral dose, sterile injectables and cephalosporins. Our products are available to veterinarians and pet owners nationwide through national and regional distributors.

Our **Strengths**

Cronus leverages our key industry network of relationships and in depth knowledge of the veterinary supply chain.

Established long term relationship with all of the national and regional veterinary distributors who have embraced our products.

Business partnerships with some of the top producers of API and CMOs in the world.

R&D and manufacturing expertise in developing differentiated and complex products.

Our **Mission**

Focus on developing alternatives to costlier and complex branded drugs yet to be genericized.

Expand access to veterinary care and increase the availability of quality generic pharmaceuticals to veterinarians and pet owners.

Improve the lives of pets through innovation and development of cost effective, quality pharmaceuticals.

To become a leading manufacturer of veterinary pharmaceuticals and positively impact the lives of animals and their caregivers.

GROWING OUR PORTFOLIO FOR YOU

CRONUSPHARMAUSA.COM

THE NEWEST **FDA REGISTERED** ANIMAL HEALTH MANUFACTURING FACILITY IN THE WORLD

RECENTLY LAUNCHED

Cropamezole™ Injection
(Atipamezole Hydrochloride)

Cropamezole™ is a dexmedetomidine and medetomidine reversing agent for use in dogs

5.0 mg/mL Sterile Injectable Solution

DOGS: Indicated for the reversal of the sedative and analgesic effects of dexmedetomidine hydrochloride, and medetomidine hydrochloride.

Cropamezole™ is administered intramuscularly (IM) for reversal of sedation and analgesia regardless of the route used for dexmedetomidine hydrochloride or medetomidine hydrochloride.

DexmedVet™ Injection
(Dexmedetomidine Hydrochloride)

DexmedVet™ is a Sedative, Analgesic, and Preanesthetic for use in dogs and cats

0.5 mg/mL Sterile Injectable Solution

DOGS & CATS: Indicated for use as a sedative and analgesic to facilitate clinical examinations, clinical procedures, minor surgical procedures, and minor dental procedures. Also indicated for use as a preanesthetic to general anesthesia. For intramuscular and intravenous use in dogs older than 16 weeks of age and for intramuscular use in cats older than 12 weeks of age.

AnaSed®-The Name You Trust Is Back!

AnaSed® Equine Injection
(Xylazine)

AnaSed® Equine Injection is a sedative and a preanesthetic to local or general anesthesia for use in horses only

100 mg/mL Sterile Injectable Solution

HORSES: AnaSed® Equine Injection is indicated as a sedative and preanesthetic. It has been successfully used when conducting various diagnostic, orthopedic and dental procedures of short duration. It may also be used as a preanesthetic to local or general anesthesia.

DetomiSed™ Injection
(Detomidine Hydrochloride)

DetomiSed™ is a synthetic alpha-2 adrenoreceptor agonist with sedative and analgesic properties for use in horses only

Sedative and Analgesic 10 mg/mL Sterile Injectable Solution

HORSES: indicated for use as a sedative and analgesic to facilitate minor surgical and diagnostic procedures in mature horses and yearlings. It has been used successfully for the following: to calm fractious horses, to provide relief from abdominal pain, to facilitate bronchoscopy, bronchoalveolar lavage, nasogastric intubation, nonreproductive rectal palpations, suturing of skin lacerations, and castrations. Additionally, an approved, local infiltration anesthetic is indicated for castration.

EnroPro™ Silver Otic
(Enrofloxacin/Silver Sulfadiazine)

EnroPro™ Silver Otic is a antibacterial-antimycotic emulsion for ototopical use in dogs

Enrofloxacin 5 mg and silver sulfadiazine (SSD) 10 mg per mL

DOGS: EnroPro™ Silver Otic is indicated as a treatment for canine otitis externa complicated by bacterial and fungal organisms susceptible to enrofloxacin and/or silver sulfadiazine (see Microbiology section).

DetomiSed™ Injection
(Detomidine Hydrochloride)

DetomiSed™ is a synthetic alpha-2 adrenoreceptor agonist with sedative and analgesic properties for use in horses only

Sedative and Analgesic 10 mg/mL Sterile Injectable Solution

HORSES: indicated for use as a sedative and analgesic to facilitate minor surgical and diagnostic procedures in mature horses and yearlings. It has been used successfully for the following: to calm fractious horses, to provide relief from abdominal pain, to facilitate bronchoscopy, bronchoalveolar lavage, nasogastric intubation, nonreproductive rectal palpations, suturing of skin lacerations, and castrations. Additionally, an approved, local infiltration anesthetic is indicated for castration.

EnroPro™ Silver Otic
(Enrofloxacin/Silver Sulfadiazine)

EnroPro™ Silver Otic is a antibacterial-antimycotic emulsion for ototopical use in dogs

Enrofloxacin 5 mg and silver sulfadiazine (SSD) 10 mg per mL

DOGS: EnroPro™ Silver Otic is indicated as a treatment for canine otitis externa complicated by bacterial and fungal organisms susceptible to enrofloxacin and/or silver sulfadiazine (see Microbiology section).

Carofenvet™ Injection
(Carprofen)

Non-steroidal anti-inflammatory (NSAID) drug

Sterile injectable solution 50 mg/mL

DOGS: In Carofenvet™ is indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

EnroPro™ 22.7 Injection
(Enrofloxacin)

EnroPro™ 22.7 is an antibacterial injectable solution for dogs only.

22.7 mg/mL Antibacterial Injectable Solution

DOGS: For the management of diseases in dogs associated with bacteria susceptible to enrofloxacin.
Enrofloxacin is a synthetic chemotherapeutic agent from the class of quinolone carboxylic acid derivatives. It has antibacterial activity against a broad spectrum of Gram negative and Gram positive bacteria (See Tables I and II).

Doraject™ Injection
(Doramectin)

Doraject™ is a highly active, broad-spectrum injectable parasiticide for cattle and swine

1% Sterile Injectable Solution, 10 mg/mL

CATTLE: Indicated for the treatment and control of the following harmful species of gastrointestinal roundworms, lungworms, eyeworms, grubs (see PRECAUTIONS), sucking lice (see PRECAUTIONS), and mange mites.

SWINE : Indicated for the treatment and control of the following species of gastrointestinal roundworms, lungworms, kidney worms, sucking lice (see PRECAUTIONS), and mange mites.

FIRST GENERIC

EnroPro™ 100 Injection
(Enrofloxacin)

EnroPro™ 100 is a sterile, ready-to-use injectable antimicrobial solution that contains enrofloxacin, a broad spectrum antimicrobial agent.

100 mg/mL Antimicrobial Injectable Solution

CATTLE - SINGLE-DOSE THERAPY: Indicated for the treatment of bovine respiratory disease (BRD) associated with Mannheimia haemolytica, Pasteurella multocida, Histophilus somni and Mycoplasma bovis in beef and non-lactating dairy cattle; and for the control of BRD in beef and non-lactating dairy cattle at high risk of developing BRD associated with M. haemolytica, P. multocida, H. somni and M. bovis.

CATTLE - MULTIPLE-DAY THERAPY: Indicated for the treatment of bovine respiratory disease (BRD) associated with Mannheimia haemolytica, Pasteurella multocida and Histophilus somni in beef and non-lactating dairy cattle.

SWINE: Indicated for the treatment and control of swine respiratory disease (SRD) associated with Actinobacillus pleuropneumoniae, Pasteurella multocida, Haemophilus parasuis, Streptococcus suis, Bordetella bronchiseptica and Mycoplasma hyopneumoniae.

Florfeniject™ Injection
(Florfenicol)

Florfeniject™ is a broad-spectrum antibiotic for the treatment of bovine respiratory disease (BRD) and bovine interdigital phlegmon (foot rot)

300 mg/mL Injectable Solution

CATTLE: For intramuscular and subcutaneous use in beef and non-lactating dairy cattle only. For the treatment of bovine respiratory disease (BRD) associated with Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni, and for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with Fusobacterium necrophorum and Bacteroides melaninogenicus.

Flunine™ Injection
(Flunixin Meglumine)

Flunine™ is a potent, non-narcotic, non-steroidal, analgesic agent for use in horses, beef, and lactating dairy cattle.

50 mg/mL Sterile Injectable Solution

HORSES: Indicated for the alleviation of inflammation and pain associated with musculoskeletal disorders in the horse. It is also Indicated for the alleviation of visceral pain associated with colic in the horse. Flunixin is four times as potent on a mg-per-mg basis as phenylbutazone as measured by the reduction in lameness and swelling in the horse. For Intravenous and Intramuscular use in horses.

CATTLE : Indicated for the control of pyrexia associated with bovine respiratory disease, endotoxemia and acute bovine mastitis. Flunixin persists in inflammatory tissues and is associated with anti-inflammatory properties which extend well beyond the period associated with detectable plasma drug concentrations. Only for Intravenous Use in Beef and Dairy Cattle. Not for Use in Dry Dairy Cows and Veal Calves.

Cronus Pharma **Product List**

NDC	Product	Strength	Species	Indication	Dosage Form	Size	Case Quantity	Approval
Companion Animal Products								
69043-046-02	Carofenvet™ Injection (Carprofen)	20 mg/mL	Canine	Anti-inflammatory Steroid	Sterile Injectable Solution	50 mL	24	Veterinary
69043-046-05	Carofenvet™ Injection (Carprofen)	50 mg/mL	Canine	Anti-inflammatory Steroid	Sterile Injectable Solution	50 mL	24	Veterinary
69043-027-60	Carprofen Chewable Tablets	25 mg	Canine	Analgesic	Tablets	60 ct	24	Veterinary
69043-027-18	Carprofen Chewable Tablets	25 mg	Canine	Analgesic	Tablets	180 ct	12	Veterinary
69043-030-60	Carprofen Chewable Tablets	75 mg	Canine	Analgesic	Tablets	60 ct	24	Veterinary
69043-030-18	Carprofen Chewable Tablets	75 mg	Canine	Analgesic	Tablets	180 ct	12	Veterinary
69043-031-60	Carprofen Chewable Tablets	100 mg	Canine	Analgesic	Tablets	60 ct	24	Veterinary
69043-031-18	Carprofen Chewable Tablets	100 mg	Canine	Analgesic	Tablets	180 ct	12	Veterinary
69043-047-02	EnroPro™ 22.7 Injection (Enrofloxacin)	22.7 mg/mL	Canine	Antibacterial	Sterile Injectable Solution	20 mL	24	Veterinary
69043-047-05	EnroPro™ 22.7 Injection (Enrofloxacin)	22.7 mg/mL	Canine	Antibacterial	Sterile Injectable Solution	50 mL	24	Veterinary
69043-056-11	EnroPro™ Silver Otic	–	Canine	Antibacterial	Drops	15 mL	12	Veterinary
69043-056-30	EnroPro™ Silver Otic	–	Canine	Antibacterial	Drops	30 mL	6	Veterinary
69043-024-11	Amoxicillin & Clavulanate Potassium Drops	62.5 mg	Canine & Feline	Antibiotic	Drops	15 mL	12	Veterinary
69043-020-21	Amoxicillin & Clavulanate Potassium Tablets	62.5 mg	Canine & Feline	Antibiotic	Tablets	210 ct	6	Veterinary
69043-021-21	Amoxicillin & Clavulanate Potassium Tablets	125 mg	Canine & Feline	Antibiotic	Tablets	210 ct	6	Veterinary
69043-022-21	Amoxicillin & Clavulanate Potassium Tablets	250 mg	Canine & Feline	Antibiotic	Tablets	210 ct	6	Veterinary
69043-023-21	Amoxicillin & Clavulanate Potassium Tablets	375 mg	Canine & Feline	Antibiotic	Tablets	210 ct	6	Veterinary
69043-013-20	Clindamycin Capsules	25 mg	Canine	Antibiotic	Capsules	200 ct	48	Veterinary
69043-014-20	Clindamycin Capsules	75 mg	Canine	Antibiotic	Capsules	200 ct	48	Veterinary
69043-015-01	Clindamycin Capsules	150 mg	Canine	Antibiotic	Capsules	100 ct	48	Veterinary
69043-015-05	Clindamycin Capsules	150 mg	Canine	Antibiotic	Capsules	500 ct	12	Veterinary
69043-016-01	Clindamycin Capsules	300 mg	Canine	Antibiotic	Capsules	100 ct	48	Veterinary
69043-012-02	Clindamycin Hydrochloride Oral Solution	25 mg/mL	Canine & Feline	Antibiotic	Drops	20 mL	72	Veterinary
69043-040-10	Methylprednisolone Tablets	1 mg	Canine & Feline	Anti-inflammatory Steroid	Tablets	100 ct	24	Veterinary
69043-040-50	Methylprednisolone Tablets	1 mg	Canine & Feline	Anti-inflammatory Steroid	Tablets	500 ct	24	Veterinary
69043-041-10	Methylprednisolone Tablets	2 mg	Canine & Feline	Anti-inflammatory Steroid	Tablets	100 ct	24	Veterinary
69043-041-50	Methylprednisolone Tablets	2 mg	Canine & Feline	Anti-inflammatory Steroid	Tablets	500 ct	24	Veterinary
69043-042-50	Methylprednisolone Tablets	4 mg	Canine & Feline	Anti-inflammatory Steroid	Tablets	100 ct	24	Veterinary
69043-042-50	Methylprednisolone Tablets	4 mg	Canine & Feline	Anti-inflammatory Steroid	Tablets	500 ct	24	Veterinary
Equine Products								
69043-043-05	AnaSed Equine Injection (Xylazine Injection)	100 mg/mL	Horses	Sedative & Preanesthetic	Sterile Injectable Solution	50 mL	24	Veterinary
69043-057-95	DetomiSed™ (Detomidine Hydrochloride)	10 mg/mL	Horses	Sedative and Analgesic	Sterile Injectable Solution	5 mL	12	Veterinary
69043-057-02	DetomiSed™ (Detomidine Hydrochloride)	10 mg/mL	Horses	Sedative and Analgesic	Sterile Injectable Solution	20 mL	12	Veterinary

Cronus Pharma **Product List**

NDC	Product	Strength	Species	Indication	Dosage Form	Size	Case Quantity	Approval
Equine Products Continued								
69043-055-25	Flunine® Injection (Flunixin Meglumine)	50 mg/mL	Horses & Cattle	Nonsteroidal Anti-Inflammatory	Sterile Injectable Solution	100 mL	12	Veterinary
69043-055-50	Flunine® Injection (Flunixin Meglumine)	50 mg/mL	Horses & Cattle	Nonsteroidal Anti-Inflammatory	Sterile Injectable Solution	250 mL	12	Veterinary
69043-043-05	Flunine® Injection (Flunixin Meglumine)	50 mg/mL	Horses & Cattle	Nonsteroidal Anti-Inflammatory	Sterile Injectable Solution	500 mL	12	Veterinary
Production Animal Products								
69043-025-89	Sulfadimethoxine 12.5% Solution	0.125	Poultry & Turkey	Antibacterial	Concentrated Solution	1 Gallon	4	Veterinary
69043-037-01	Doramectin Injection (Doraject)	10 mg/mL	Cattle	Parasiticide	Sterile Injectable Solution	100 mL	12	Veterinary
69043-037-25	Doramectin Injection (Doraject)	10 mg/mL	Cattle	Parasiticide	Sterile Injectable Solution	250 mL	12	Veterinary
69043-037-05	Doramectin Injection (Doraject)	10 mg/mL	Cattle	Parasiticide	Sterile Injectable Solution	500 mL	12	Veterinary
69043-048-10	EnroPro™ 100 (enrofloxacin)	100 mg/mL	Cattle & Swine	Antimicrobial	Sterile Injectable Solution	100 mL	12	Veterinary
69043-048-25	EnroPro™ 100 (enrofloxacin)	100 mg/mL	Cattle & Swine	Antimicrobial	Sterile Injectable Solution	250 mL	12	Veterinary
69043-048-50	EnroPro™ 100 (enrofloxacin)	100 mg/mL	Cattle & Swine	Antimicrobial	Sterile Injectable Solution	500 mL	12	Veterinary
69043-044-10	Florfeniject™ Injection (Florfenicol)	300 mg/mL	Cattle	Antibiotic	Sterile Injectable Solution	100 mL	24	Veterinary
69043-044-25	Florfeniject™ Injection (Florfenicol)	300 mg/mL	Cattle	Antibiotic	Sterile Injectable Solution	250 mL	12	Veterinary
69043-044-50	Florfeniject™ Injection (Florfenicol)	300 mg/mL	Cattle	Antibiotic	Sterile Injectable Solution	500 mL	12	Veterinary
69043-039-10	Atipamezole Injection (Cropamezole)	5 mg/mL	Canine	Sedative & Analgesic	Sterile Injectable Solution	10 mL	24	Veterinary
69043-038-10	Dexmedetodimine Injection (DexmedVet)	0.5 mg/mL (5 mg/10 mL)	Canine & Feline	Sedative & Analgesic	Sterile Injectable Solution	10 mL	24	Veterinary
69043-043-05	Xylazine Injection	100 mg/mL	Horses	Sedative & Preanesthetic	Sterile Injectable Solution	50 mL	24	Veterinary
Human Products								
69043-006-01	Cefpodoxime Tablets	100 mg	Human	Antibiotic	Tablets	100 ct	48	Human
69043-007-01	Cefpodoxime Tablets	200 mg	Human	Antibiotic	Tablets	100 ct	24	Human
69043-008-01	Cephalexin Capsules	250 mg	Human	Antibiotic	Capsules	100 ct	12	Human
69043-008-05	Cephalexin Capsules	250 mg	Human	Antibiotic	Capsules	500 ct	12	Human
69043-009-01	Cephalexin Capsules	500 mg	Human	Antibiotic	Capsules	100 ct	12	Human
69043-009-05	Cephalexin Capsules	500 mg	Human	Antibiotic	Capsules	500 ct	12	Human
69043-011-05	SMZ-TMP Tablets	800 mg & 160 mg	Human	Antibacterial	Tablets	500 ct	12	Human

Companion Animal Product Summary

Amoxicillin & Clavulanate Potassium Drops

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-024-11	Antibiotic	15 mL — 62.5 mg	12	

Amoxicillin & Clavulanate Potassium Tablets

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-020-21	Antibiotic	210 ct — 62.5 mg	6	
69043-021-21	Antibiotic	210 ct — 125 mg	6	
69043-022-21	Antibiotic	210 ct — 250 mg	6	
69043-023-21	Antibiotic	210 ct — 375 mg	6	

Atipamezole Injection
(Cropamezole)

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-039-10	Sedative & Analgesic	10 mL — 5 mg/mL	24	

Carofenvet™ Injection
(Carprofen)

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-046-02	Anti-inflammatory Steroid	20 mL — 50 mg/mL	24	
69043-046-05	Anti-inflammatory Steroid	50 mL — 50 mg/mL	24	

Companion Animal Product Summary

Carprofen Chewable Tablets

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-027-60	Analgesic	60 ct — 25 mg	24	
69043-027-18	Analgesic	180 ct — 25 mg	12	
69043-030-60	Analgesic	60 ct — 75 mg	24	
69043-030-18	Analgesic	180 ct — 75 mg	12	
69043-031-60	Analgesic	60 ct — 100 mg	24	
69043-031-18	Analgesic	180 ct — 100 mg	12	

Clindamycin Capsules

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-013-20	Antibiotic	200 ct — 25 mg	48	
69043-014-20	Antibiotic	200 ct — 75 mg	48	
69043-015-01	Antibiotic	100 ct — 150 mg	48	
69043-015-05	Antibiotic	500 ct — 150 mg	12	
69043-016-01	Antibiotic	100 ct — 300 mg	48	

Clindamycin Hydrochloride Oral Solution

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-012-02	Antibiotic	20 mL — 25 mg/mL	72	

Dexmedetodimine Injection
(DexmedVet)

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-038-10	Sedative & Analgesic	10 mL — 0.5 mg/mL (5 mg/10 mL)	24	

Companion Animal Product Summary

EnroPro™ 22.7 Injection
(Enrofloxacin)

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-047-02	Antibacterial	20 mL	24	
69043-047-05	Antibacterial	50 mL	24	

EnroPro™ Silver Otic
(Enrofloxacin/Silver Sulfadiazine)

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-056-12	Antibiotic	15 mL	12	
69043-056-30	Antibiotic	30 mL	6	

Methylprednisolone
(Canine)

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-040-10	Anti-inflammatory Steroid	100 ct — 1 mg	24	
69043-040-50	Anti-inflammatory Steroid	500 ct — 1 mg	24	
69043-041-10	Anti-inflammatory Steroid	100 ct — 2 mg	24	
69043-041-50	Anti-inflammatory Steroid	500 ct — 2 mg	24	
69043-042-10	Anti-inflammatory Steroid	100 ct — 4 mg	24	
69043-042-50	Anti-inflammatory Steroid	500 ct — 4 mg	24	

Equine Product Summary

AnaSed® Equine Injection
(Xylazine Injection)

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-043-05	Sedative and Preanesthetic	50 mL — 100 mg/mL	24	

DetomiSed™
(Detomidine Hydrochloride)

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-057-95	Sedative and Analgesic	5 mL — 10 mg/mL	–	
69043-057-02	Sedative and Analgesic	20 mL — 10 mg/mL	–	

Flunine™ Injection
(Flunixin Meglumine)

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-055-10	Nonsteroidal Anti-Inflammatory	100 mL — 50 mg/mL	12	
69043-055-25	Nonsteroidal Anti-Inflammatory	250 mL — 50 mg/mL	12	
69043-055-50	Nonsteroidal Anti-Inflammatory	500 mL — 50 mg/mL	12	

Production Animal Product Summary

Doramectin Injection
(Doraject)

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-037-01	Parasiticide	100 mL — 10 mg/mL	12	
69043-037-25	Parasiticide	250 mL — 10 mg/mL	12	
69043-037-05	Parasiticide	500 mL — 10 mg/mL	12	

EnroPro™ 100
(Enrofloxacin)

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-048-10	Antimicrobial	100 mL — 100 mg/mL	24	
69043-048-25	Antimicrobial	250 mL — 100 mg/mL	12	
69043-048-50	Antimicrobial	500 mL — 100 mg/mL	12	

Florfeniject™ Injection
(Florfenicol)

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-044-10	Antibiotic	100 mL — 300 mg/mL	24	
69043-044-25	Antibiotic	250 mL — 300 mg/mL	12	
69043-044-50	Antibiotic	500 mL — 300 mg/mL	12	

Sulfadimethoxine 12.5% Solution

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY	SPECIES
69043-025-89	Antibacterial	1 Gallon — 12.50%	4	

Human Product Summary

Cefpodoxime Tablets

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY
69043-006-01	Antibiotic	100 ct — 100 mg	48
69043-007-01	Antibiotic	100 ct — 200 mg	24

Cephalexin Capsules

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY
69043-008-01	Antibiotic	100 ct — 250 mg	12
69043-008-05	Antibiotic	500 ct — 250 mg	12
69043-009-01	Antibiotic	100 ct — 500 mg	12
69043-009-05	Antibiotic	500 ct — 500 mg	12

SMZ-TMP Tablets

NDC NO.	INDICATION	SIZE & STRENGTH	CASE QUANTITY
69043-011-05	Antibacterial	500 ct — 800 mg & 160 mg	12

Amoxicillin and Clavulanate Potassium for Oral Suspension Drops

A broad-spectrum antibiotic clinically proven to treat many bacterial infections in dogs and cats

DOGS: Indicated in the treatment of periodontal and skin and soft tissue infections such as wounds, abscesses, cellulitis, and superficial/juvenile and deep pyoderma due to susceptible strains of bacteria.

CATS: Indicated in the treatment of urinary tract infections (cystitis) and skin and soft tissue infections such as wounds, abscesses, and cellulitis/dermatitis due to susceptible strains of bacteria.

FDA approved under ANADA #200-709; this product has been shown to be bioequivalent to the reference product, Clavamox®.

Available in:

- 15 mL dropper bottles.
- Bubble gum flavor

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

Amoxicillin and Clavulanate Potassium Tablets

A broad-spectrum antibiotic clinically proven to treat many bacterial infections in dogs and cats

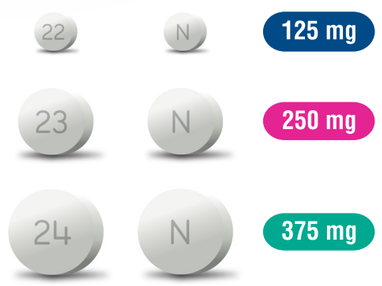
DOGS: Indicated in the treatment of periodontal and skin and soft tissue infections such as wounds, abscesses, cellulitis, and superficial/juvenile and deep pyoderma due to susceptible strains of bacteria.

CATS: Indicated in the treatment of urinary tract infections (cystitis) and skin and soft tissue infections such as wounds, abscesses, and cellulitis/dermatitis due to susceptible strains of bacteria.

FDA approved under ANADA #200-702; this product has been shown to be bioequivalent to the reference product, Clavamox®.

Available in:

- 62.5 mg, 125 mg, 250 mg, and 375 mg tablets supplied in foil strip packs.
- Each carton holds 15 foil strip packs with 14 tablets per strip (210 tablets per carton).



Approximately to Scale

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

Carofenvet™ Injection
(Carprofen)

Non-steroidal anti-inflammatory (NSAID) drug

Sterile injectable solution 50 mg/mL

INDICATIONS: Carofenvet™ is indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

Carofenvet™ Injectable is a sterile solution containing carprofen, a non-steroidal anti-inflammatory drug (NSAID) of the propionic acid class that includes ibuprofen, naproxen, and ketoprofen.

For subcutaneous use in dogs only

FDA Approved under ANADA#200-782; this product is considered a generic equivalent to the reference product, Rimadyl injection.

Available in:

- 20 mL and 50 mL amber, glass, sterile, multi dose vials.

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

Carprofen Chewable Tablets

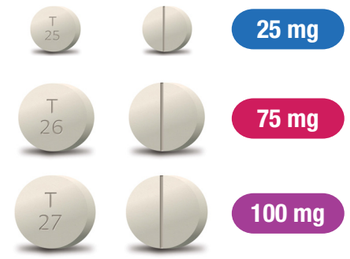
Convenient and effective pain relief for dogs

INDICATION: Proven safe for the treatment of pain, soreness, and inflammation associated with osteoarthritis and control of post-operative pain.

FDA approved under ANADA #200-687; this product has been shown to be bioequivalent to the reference product, Rimadyl®.

Available in:

- 60 mg count bottles.
- Available in 60 and 180 count bottles.
- Chicken liver flavored.



Approximately to Scale

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

Cropamezole™ Injection
(Atipamezole Hydrochloride)

Cropamezole™ is a dexmedetomidine and medetomidine reversing agent for use in dogs

Sedative and Analgesic Reversing Agent
5.0 mg/mL Sterile Injectable Solution

DOGS: Indicated for the reversal of the sedative and analgesic effects of dexmedetomidine hydrochloride, and medetomidine hydrochloride.

Cropamezole™ is administered intramuscularly (IM) for reversal of sedation and analgesia regardless of the route used for dexmedetomidine hydrochloride or medetomidine hydrochloride.

For use in dogs older than four months of age and weighing more than 4.4 lbs (2 kg).

Each mL contains 5.0 mg atipamezole hydrochloride, 1.0 mg methylparaben (NF), 8.5 mg sodium chloride (USP), and water for injection (USP).

FDA approved under ANADA #200-753; this product is considered a generic equivalent to the reference product, Antisedan®.

Available in:
• 10 mL multi-dose, rubber-stoppered glass vials.

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

Clindamycin Hyrdrochloride Capsules

Oral antibiotic to treat soft tissue, dental and bone infections caused by susceptible strains of bacteria in dogs

The only FDA veterinary approval of all four dosage strengths: 25 mg, 75 mg, 150 mg & 300 mg

Clindamycin Hydrochloride Capsules, USP for use in dogs only, are indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below:

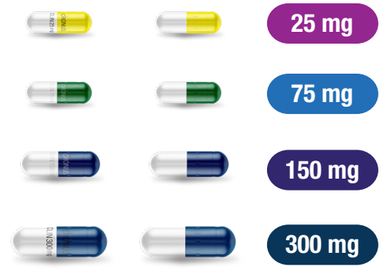
Skin infections (wounds and abscesses) due to coagulase positive staphylococci (Staphylococcus aureus or Staphylococcus intermedius).

Deep wounds and abscesses due to Bacteroides fragilis, Prevotella melaninogenicus, Fusobacterium necrophorum and Clostridium perfringens.

Dental infections due to Staphylococcus aureus, Bacteroides fragilis, Prevotella melaninogenicus, Fusobacterium necrophorum and Clostridium perfringens.

Osteomyelitis due to Staphylococcus aureus, Bacteroides fragilis, Prevotella melaninogenicus, Fusobacterium necrophorum and Clostridium perfringens.

FDA approved under ANADA #200-298, this product is considered bioequivalent to the reference product, Antirobe®.



Approximately to Scale

Available in:
- 25 mg – 200 count bottles
- 75 mg – 200 count bottles
- 150 mg – 100 & 500 count bottles
- 300 mg – 100 count bottles

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

Clindamycin Hydrochloride Oral Solution

Oral solution antibiotic to treat soft tissue, dental and bone infections caused by susceptible strains of bacteria in dogs and cats

Clindamycin Hydrochloride Oral Solution (for use in dogs and cats) is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms the specific conditions listed below:

DOGS: Skin infections (wounds and abscesses) due to coagulase positive staphylococci (Staphylococcus aureus or Staphylococcus intermedius).

Deep wounds and abscesses due to Bacteroides fragilis, Prevotella melaninogenicus, Fusobacterium necrophorum and Clostridium perfringens.

Dental infections due to Staphylococcus aureus, Bacteroides fragilis, Prevotella melaninogenicus, Fusobacterium necrophorum and Clostridium perfringens.

Osteomyelitis due to Staphylococcus aureus, Bacteroides fragilis, Prevotella melaninogenicus, Fusobacterium necrophorum and Clostridium perfringens.

CATS: Skin infections (wounds and abscesses) due to Staphylococcus aureus, Staphylococcus intermedius, Streptococcus spp.

Deep wounds and abscesses due to Clostridium perfringens and Bacteroides fragilis.

Dental infections due to Staphylococcus aureus, Staphylococcus intermedius, Streptococcus spp., Clostridium perfringens and Bacteroides fragilis.

FDA approved under ANADA #200-193; this product is considered a generic equivalent to the reference product, Antirobe®.

Available in:

- 30 mL dropper bottle.

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

DexmedVet™ Injection (Dexmedetomidine Hydrochloride)

DexmedVet™ is a Sedative, Analgesic, and Preanesthetic for use in dogs and cats

0.5 mg/mL Sterile Injectable Solution

DOGS & CATS: Indicated for use as a sedative and analgesic to facilitate clinical examinations, clinical procedures, minor surgical procedures, and minor dental procedures. Also indicated for use as a preanesthetic to general anesthesia. For intramuscular and intravenous use in dogs older than 16 weeks of age and for intramuscular use in cats older than 12 weeks of age.

The use of DexmedVet™ as a preanesthetic markedly reduces anesthetic requirements in dogs.

Each mL contains 0.5 mg dexmedetomidine hydrochloride, 1.6 mg methylparaben (NF), 0.2 mg propylparaben (NF), 9.0 mg sodium chloride (USP), and water for injection (USP), q.s.

FDA approved under ANADA #200-752; this product is considered a generic equivalent to the reference product, Dexdomitor®.

Available in:

- 10 mL multi-dose, rubber-stoppered glass vials.

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

EnroPro™ 22.7 Injection
(Enrofloxacin)

EnroPro™ 22.7 is an antibacterial injectable solution for dogs only.

22.7 mg/mL Antibacterial Injectable Solution

INDICATIONS: For the management of diseases in dogs associated with bacteria susceptible to enrofloxacin.

Enrofloxacin is a synthetic chemotherapeutic agent from the class of quinolone carboxylic acid derivatives. It has antibacterial activity against a broad spectrum of Gram negative and Gram positive bacteria (See Tables I and II).

Each mL of injectable solution contains: enrofloxacin 22.7 mg, n-butyl alcohol 30 mg, potassium hydroxide for pH adjustment and water for injection, q.s.

Approved by FDA under ANADA #200-764: this product is considered a generic equivalent to the reference product, Baytril™ 22.7.

Available in:
• 20 mL and 50 mL multi-dose vials.

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

EnroPro™ Silver Otic
(Enrofloxacin/Silver Sulfadiazine)

EnroPro™ Silver Otic is a antibacterial-antimycotic emulsion for ototopical use in dogs.

Enrofloxacin 5 mg and silver sulfadiazine (SSD) 10 mg per mL.

INDICATIONS: A treatment for canine otitis externa complicated by bacterial and fungal organisms susceptible to enrofloxacin and/or silver sulfadiazine.

Bactericidal with activity against a broad spectrum of both Gram negative and Gram positive bacteria.

Silver sulfadiazine (SSD) is synthesized from silver nitrate and sodium sulfadiazine[4] and is also an effective antimycotic.[5,6]

The combination of enrofloxacin and silver sulfadiazine targets both bacterial and fungal infections.

Effective when used as a treatment for canine otitis externa associated with one or more of the following organisms: *Malassezia pachydermatis, coagulase-positive Staphylococcus spp., Pseudomonas aeruginosa, Enterobacter spp., Proteus mirabilis, Streptococci spp., Aeromonas hydrophila, Aspergillus spp., Klebsiella pneumoniae,* and *Candida albicans*.

Approved by FDA under ANADA # 200-782; this product is the generic equivalent of the referenced product, Baytril® Otic.

Available in:
• 15 mL in 12 bottle carton and 30 mL in 6 bottle carton of dropper bottles.

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

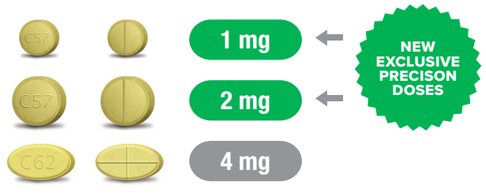
Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

Methylprednisolone Tablets, USP

Methylprednisolone is a potent glucocorticoid and anti-inflammatory agent for use in dogs and cats

Improved dosing convenience with exclusive precision 1 mg & 2 mg doses



Approximately to Scale

INDICATIONS: The indications are the same as those for other anti-inflammatory steroids and comprise the various collagen, dermal, allergic, ocular, otic and musculoskeletal conditions known to be responsive to the anti-inflammatory corticosteroids.

It has a greater anti-inflammatory potency than prednisolone and is less likely to induce sodium and water retention.

Its advantage over the older corticoids lies in its ability to achieve equal anti-inflammatory effect with a lower dose, while at the same time enhancing the split between anti-inflammatory and mineralocorticoid activities. [1, 2, 3]

- Dermal conditions, such as non-specific eczema and summer dermatics. [1, 2, 4]
- Allergic manifestations, such as acute urticaria, allergic dermatitis, drug and serum reactions, non-specific pruritus, bronchial asthma and pollen sensitivities. [1, 2, 3, 4, 5]
- Ocular Conditions, such as iritis, iridocyclitis, secondary glaucoma, uveitis and chlorioretinitis. [1, 3, 4, 5]
- Otic Conditions, such as otitis externa. [4]
- Musculoskeletal Conditions, such as myositis, rheumatoid arthritis, osteoarthritis and bursitis. [1, 2, 3, 4, 5]
- Various chronic or recurrent diseases of unknown etiology such as ulcerative colitis and nephrosis. [1, 2, 3, 5]

In the therapeutic management of animals with chronic diseases, such as rheumatoid arthritis, methylprednisolone should be regarded as a highly valuable adjunct, to be used in conjunction with but not as a replacement for standard therapeutic measures.

FDA approved under NADA #135-771.

Available in:
- 1 mg, 2 mg (yellow round) and 4 mg (yellow oval) scored tablets in bottles of 100 and 500.

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

AnaSed®-The Name You Trust Is Back!

AnaSed® Equine Injection (Xylazine)

AnaSed® Equine Injection is a sedative and a preanesthetic to local or general anesthesia for use in horses only

100 mg/mL Sterile Injectable Solution

INDICATIONS: For use as a sedative and preanesthetic.

It has been successfully used when conducting various diagnostic, orthopedic and dental procedures of short duration. It may also be used as a preanesthetic to local or general anesthesia.

At the recommended dosages AnaSed® may be used in conjunction with local anesthetics, such as procaine and lidocaine.

AnaSed® has been successfully used as a preanesthetic agent for sodium pentobarbital, sodium thiopental, sodium thiamylal, nitrous oxide, ether, halothane, guaifenesin and methoxyflurane anesthesia.

For intravenous (IV) or intramuscular (IM) use.

Each mL Contains: Xylazine HCl equivalent to 100 mg Xylazine base (see additional details on package insert).

FDA approved under NADA #140-442.

Available in:
- 20 mL and 50 mL multi-dose, rubber-stoppered glass vials.

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

DetomiSed™ Injection
(Detomidine Hydrochloride)

DetomiSed™ is a synthetic alpha-2 adrenoreceptor agonist with sedative and analgesic properties for use in horses only

10 mg/mL Sterile Injectable Solution

INDICATIONS: For use as a sedative and analgesic to facilitate minor surgical and diagnostic procedures in mature horses and yearlings. It has been used successfully for the following: to calm fractious horses, to provide relief from abdominal pain, to facilitate bronchoscopy, bronchoalveolar lavage, nasogastric intubation, nonreproductive rectal palpations, suturing of skin lacerations, and castrations. Additionally, an approved, local infiltration anesthetic is indicated for castration.

DetomiSed™, a non-narcotic sedative and analgesic, is a potent α2-adrenoreceptor agonist which produces sedation and superficial and visceral analgesia which is dose dependent in its depth and duration.

Each mL of DetomiSed™ contains 10.0 mg detomidine hydrochloride, 1.0 mg methyl paraben, 5.9 mg sodium chloride, and water for injection, q.s.

Approved by FDA under ANADA #200-611; this product is considered a generic equivalent to the reference product, Dormosedan®.

Available in:
• 5 mL and 20 mL multi-dose vials.

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

 01.19.25

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

Flunine™ Injection
(Flunixin Meglumine)

Flunine™ is a potent, non-narcotic, non-steroidal, analgesic agent for use in horses, beef, and lactating dairy cattle.

50 mg/mL Sterile Injectable Solution

INDICATIONS
HORSES: Indicated for the alleviation of inflammation and pain associated with musculoskeletal disorders in the horse. It is also Indicated for the alleviation of visceral pain associated with colic in the horse. Flunixin is four times as potent on a mg-per-mg basis as phenylbutazone as measured by the reduction in lameness and swelling in the horse. For Intravenous and Intramuscular use in horses.

CATTLE: Indicated for the control of pyrexia associated with bovine respiratory disease, endotoxemia and acute bovine mastitis. Flunixin persists in inflammatory tissues and is associated with anti-inflammatory properties which extend well beyond the period associated with detectable plasma drug concentrations. Only for Intravenous Use in Beef and Dairy Cattle. Not for Use in Dry Dairy Cows and Veal Calves.

FDA approved under ANADA #200-781; this product is considered a generic equivalent to the reference product, Banamine®.

Available in:
• 100 mL, 250 mL and 500 mL multi-dose, rubber-stoppered, amber glass vials.

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

 01.19.25

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

Doraject™ Injection
(Doramectin)

Doraject™ is a highly active, broad-spectrum injectable parasiticide for cattle and swine

Antiparasitic
1% Sterile Injectable Solution, 10 mg/mL

One dose of Doraject™ effectively treats and controls a wide range of roundworm and arthropod parasites that impair the health and productivity of cattle and swine.

Doraject™ is a ready-to-use, colorless to pale yellow, sterile solution containing 1% w/v doramectin (10 mg/mL).

CATTLE: Indicated for the treatment and control of the following harmful species of gastrointestinal roundworms, lungworms, eyeworms, grubs (see PRECAUTIONS), sucking lice (see PRECAUTIONS), and mange mites.

SWINE: Indicated for the treatment and control of the following species of gastrointestinal roundworms, lungworms, kidney worms, sucking lice (see PRECAUTIONS), and mange mites.

FDA approved under ANADA #200-750; this product is considered a generic equivalent to the reference product, Dectomax®.

Available in:
- 100 mL, 250 mL and 500 mL multi-dose, rubber-stoppered glass vials.

FIRST GENERIC

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

EnroPro™ 100 Injection
(Enrofloxacin)

EnroPro™ 100 is a sterile, ready-to-use injectable antimicrobial solution that contains enrofloxacin, a broad spectrum antimicrobial agent.

100 mg/mL Antimicrobial Injectable Solution

INDICATIONS: Indicated for the treatment of bovine respiratory disease (BRD), for the treatment and control of swine respiratory disease (SRD).

Each mL of EnroPro™ 100 contains 100 mg of enrofloxacin. Excipients are L-arginine base 200 mg, n-butyl alcohol 30 mg, benzyl alcohol (as a preservative) 20 mg and water for injection q.s.

CATTLE - Single-Dose Therapy: Indicated for the treatment of bovine respiratory disease (BRD) associated with Mannheimia haemolytica, Pasteurella multocida, Histophilus somni and Mycoplasma bovis in beef and non-lactating dairy cattle; and for the control of BRD in beef and non-lactating dairy cattle at high risk of developing BRD associated with M. haemolytica, P. multocida, H. somni and M. bovis.

CATTLE - Multiple-Day Therapy: Indicated for the treatment of bovine respiratory disease (BRD) associated with Mannheimia haemolytica, Pasteurella multocida and Histophilus somni in beef and non-lactating dairy cattle.

SWINE: Indicated for the treatment and control of swine respiratory disease (SRD) associated with Actinobacillus pleuropneumoniae, Pasteurella multocida, Haemophilus parasuis, Streptococcus suis, Bordetella bronchiseptica and Mycoplasma hyopneumoniae. Also indicated for the control of colibacillosis in groups or pens of weaned pigs where colibacillosis associated with Escherichia coli has been diagnosed.

Approved by FDA under ANADA #200-765; this product is considered a generic equivalent to the reference product, Baytril® 100

Available in:
- 100 mL, 250 mL, and 500 mL multi-dose vials.

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

Florfeniject™ Injection
(Florfenicol)

Florfeniject™ is a broad-spectrum antibiotic for the treatment of bovine respiratory disease (BRD) and bovine interdigital phlegmon (foot rot)

300 mg/mL Injectable Solution

INDICATIONS: For intramuscular and subcutaneous use in beef and non-lactating dairy cattle only.

For the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*, and for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.

Also, it is indicated for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*.

Each milliliter contains 300 mg of florfenicol, 250 mg N-methyl-2-pyrrolidone (NMP), 150 mg propylene glycol, and polyethylene glycol qs.

Approved by FDA under ANADA #200-760; this product is considered a generic equivalent to the reference product, Nuflor®.

Available in:
100 mL, 250 mL, and 500 mL glass sterile multi-dose vials.

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

Approved by FDA under ANADA #200-760; this product is considered a generic equivalent to the reference product, Nuflor®.

Sulfadimethoxine Concentrated Solution 12.5%

Sulfadimethoxine Concentrated Solution is a concentrated (12.5%), broad-spectrum antibacterial oral solution for use in drinking water to control a variety of diseases in chickens, turkeys and cattle.

PROTECT FROM LIGHT

BROILER AND REPLACEMENT CHICKENS: Use for the treatment of disease outbreaks of coccidiosis, fowl cholera, and infectious coryza.

MEAT PRODUCING TURKEYS: Use for the treatment of disease outbreaks of coccidiosis and fowl cholera.

DAIRY CALVES, DAIRY HEIFERS AND BEEF CATTLE: Use for the treatment of shipping fever complex and bacterial pneumonia associated with Pasteurella spp. sensitive to sulfadimethoxine, calf diphtheria and foot rot associated with Fusobacterium necrophorum (Sphaerophorus necrophorus) sensitive to sulfadimethoxine.

Administer as a drench to treat individual animals or dispense through a water proportioner for mass medication of flocks or herds.

FDA approved under ANADA #200-165; this product is considered bioequivalent to the reference product, Albon® 12.5% Solution.

Available in:
• 1 gallon (3.785 liters) bottle.

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.
1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

Cefpodoxime Proxetil Tablets, USP

Cefpodoxime is an oral, third-generation cephalosporin antibiotic. It is active against most Gram-positive and Gram-negative organisms

It is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

100 mg

200 mg

Approximately to Scale

Acute otitis media caused by *Streptococcus pneumoniae* (excluding penicillin-resistant strains), *Streptococcus pyogenes, Haemophilus influenzae* (including beta-lactamase-producing strains), or *Moraxella (Branhamella) catarrhalis* (including beta-lactamase-producing strains).

Pharyngitis and/or tonsillitis caused by *Streptococcus pyogenes*.

Community-acquired pneumonia caused by *S. pneumoniae or H. Influenzae* (including beta-lactamase-producing strains).

Acute bacterial exacerbation of chronic bronchitis caused by *S. pneumoniae, H. influenzae* (non-beta-lactamase-producing strains only), or *M. catarrhalis*. Data are insufficient at this time to establish efficacy in patients with acute bacterial exacerbations of chronic bronchitis caused by beta-lactamase-producing strains of *H. influenzae*.

Acute, uncomplicated urethral and cervical gonorrhea caused by *Neisseria gonorrhoeae* (including penicillinase-producing strains).

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (including penicillinase-producing strains) or *Streptococcus pyogenes*. Abscesses should be surgically drained as clinically indicated.

Acute maxillary sinusitis caused by *Haemophilus influenzae* (including beta-lactamase-producing strains), *Streptococcus pneumoniae, and Moraxella catarrhalis*.

Uncomplicated urinary tract infections (cystitis) caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis*, or *Staphylococcus saprophyticus*.

FDA approved under ANDA 065370, this product has been shown to be bioequivalent to the reference product, Vantin®.

Available in:

- 100 mg and 200 mg film coated tablets in 100 count bottles.

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.

1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

 01.19.25

Cephalexin Capsules, USP

Cephalexin is a broad spectrum antibiotic used in the treatment of some respiratory tract infections, urinary tract infections or skin and soft tissue infections such as wounds, abscesses and lacerations including:

250 mg

500 mg

Approximately to Scale

Respiratory tract infections caused by susceptible isolates of *Streptococcus pneumoniae* and *Streptococcus pyogenes.*

Otitis media caused by susceptible isolates of *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Streptococcus pyogenes,* and *Moraxella catarrhalis.*

Skin and skin structure infections caused by susceptible isolates of the following Gram-positive bacteria: *Staphylococcus aureus* and *Streptococcus pyogenes.*

Bone infections caused by susceptible isolates of *Staphylococcus aureus* and *Proteus mirabilis.*

Genitourinary tract infections, including acute prostatitis, caused by susceptible isolates of *Escherichia coli, Proteus mirabilis*, and *Klebsiella pneumoniae.*

FDA approved under ANDA 065253, this product has been shown to be bioequivalent to the reference product, Keflex®.

Available in:

- 250 mg and 500 mg capsules in 500 count bottles.
- 100 mg and 200 mg capsules in 100 count bottles.

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.

1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

 01.19.25

Sulfamethoxazole and Trimethoprim Tablets, USP

Sulfamethoxazole Trimethoprim Tablets are potentiated sulfonamide broad spectrum antimicrobial agents used to treat susceptible bacterial infections

To reduce the development of drug-resistant bacteria and maintain the effectiveness of sulfamethoxazole and trimethoprim tablets and other antibacterial drugs, sulfamethoxazole and trimethoprim tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria including:

Urinary Tract Infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella species, Enterobacter species, Morganella morganii, Proteus mirabilis* and *Proteus vulgaris*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

Acute Otitis Media in pediatric patients due to susceptible strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* when in the judgment of the physician sulfamethoxazole and trimethoprim tablets offers some advantage over the use of other antimicrobial agents. Sulfamethoxazole and trimethoprim tablets are not indicated for prophylactic or prolonged administration in otitis media at any age.

Acute Exacerbations of Chronic Bronchitis in Adults due to susceptible strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* when a physician deems that sulfamethoxazole and trimethoprim tablets could offer some advantage over the use of a single antimicrobial agent.

Shigellosis: For the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Pneumocystis jirovecii Pneumonia and for prophylaxis against *P. jirovecii* pneumonia in individuals who are immunosuppressed and considered to be at an increased risk of developing *P. jirovecii* pneumonia.

Traveler's Diarrhea in Adults due to susceptible strains of enterotoxigenic *E. coli*.

FDA approved under ANDA 090624, this product has been shown to be bioequivalent to the reference product, Bactrim and Bactrim DS.

Available in:

- 400 mg/80 mg tablets in 100 count bottles.
- 800 mg/160 mg double strength tablets in 500 count bottles.

Approximately to Scale

Cronus Pharma

www.cronuspharmausa.com

For more information about Cronus Pharma products please contact your authorized distributor.

1 (844) 227-6687

Cronus Pharma LLC is a fully integrated R&D, manufacturing, and marketing animal health pharmaceutical company headquartered in East Brunswick, NJ. Dedicated to providing quality and cost-effective pharmaceuticals to the U.S. animal health market, our products are accessible to all veterinarians and pet owners through national and regional distributors.

Please refer to the Package Insert for complete prescribing instructions, precautions, and full safety information.

AMOXICILLIN AND CLAVULANATE POTASSIUM FOR ORAL SUSPENSION DROPS

For veterinary oral suspension
For use in dogs and cats

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Amoxicillin trihydrate/clavulanate potassium is an orally administered formulation comprised of the broad-spectrum antibiotic amoxicillin trihydrate and the β-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid).

Amoxicillin trihydrate is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram-negative, aerobic and anaerobic microorganisms. It does not resist destruction by β-lactamases; therefore, it is not effective against β-lactamase-producing bacteria. Chemically, it is D(-)-α-amino-p-hydroxybenzyl penicillin trihydrate.

Clavulanic acid, an inhibitor of β-lactamase enzymes, is produced by the fermentation of *Streptomyces clavuligerus*. Clavulanic acid by itself has only weak antibacterial activity. Chemically, clavulanate potassium is potassium z-(3R,5R)-2-β-hydroxyethylidene clavam-3-carboxylate.

CLINICAL PHARMACOLOGY: Amoxicillin and Clavulanate Potassium for Oral Suspension is stable in the presence of gastric acid and is not significantly influenced by gastric or intestinal contents. The 2 components are rapidly absorbed resulting in amoxicillin and clavulanic acid concentrations in serum, urine, and tissues similar to those produced when each is administered alone.

Amoxicillin and clavulanic acid diffuse readily into most body tissues and fluids with the exception of brain and spinal fluid, which amoxicillin penetrates adequately when meninges are inflamed. Most of the amoxicillin is excreted unchanged in the urine. Clavulanic acid's penetration into spinal fluid is unknown at this time. Approximately 15% of the administered dose of clavulanic acid is excreted in the urine within the first 6 hours.

Amoxicillin and Clavulanate Potassium for Oral Suspension combines the distinctive properties of a broad-spectrum antibiotic and a β-lactamase inhibitor to effectively extend the antibacterial spectrum of amoxicillin to include β-lactamase-producing as well as non-β-lactamase-producing aerobic and anaerobic organisms.

MICROBIOLOGY: Amoxicillin is bactericidal in action and acts through the inhibition of biosynthesis of cell wall mucopeptide of susceptible organisms. The action of clavulanic acid extends the antimicrobial spectrum of amoxicillin to include organisms resistant to amoxicillin and other β-lactam antibiotics.

Amoxicillin/clavulanate has been shown to have a wide range of activity which includes β-lactamase-producing strains of both gram-positive and gram-negative aerobes, facultative anaerobes, and obligate anaerobes. Many strains of the following organisms, including β-lactamase-producing strains, isolated from veterinary sources, were found to be susceptible to amoxicillin/clavulanate in vitro but the clinical significance of this activity has not been demonstrated for some of these organisms in animals. Aerobic bacteria, including *Staphylococcus aureus1,* β-lactamase-producing *Staphylococcus aureus1* (penicillin resistant), *Staphylococcus species1, Staphylococcus epidermidis, Staphylococcus intermedius, Streptococcus faecalis, Streptococcus species1, Corynebacterium pyogenes, Corynebacterium species, Erysipelothrix rhusiopathiae, Bordetella bronchiseptica, Escherichia coli1, Proteus mirabilis, Proteus species, Enterobacter species, Klebsiella pneumoniae, Salmonella dublin, Salmonella typhimurium, Pasteurella multocida1, Pasteurella haemolytica, Pasteurella species*[1].

[1]The susceptibility of these organisms has also been demonstrated in in *vivo* studies.

Studies have demonstrated that both aerobic and anaerobic flora are isolated from gingival cultures of dogs with clinical evidence of periodontal disease. Both gram-positive and gram-negative aerobic and anaerobic subgingival isolates indicate sensitivity to amoxicillin/clavulanic acid during antimicrobial susceptibility testing.

SUSCEPTIBILITY TEST: The recommended quantitative disc susceptibility method (FEDERAL REGISTER 37:20527–29; Bauer AW, Kirby WMM, Sherris JC, *et al*: Antibiotic susceptibility testing by standardized single disc method. *Am J Clin Path* 45:493, 1966) utilized 30 mcg Augmentin® (AMC) discs for estimating the susceptibility of bacteria to amoxicillin and clavulanate potassium tablets and amoxicillin and clavulanate potassium for oral suspension.

INDICATIONS AND USAGE: Amoxicillin and Clavulanate Potassium for Oral Suspension drops are indicated in the treatment of:

Dogs: Skin and soft tissue infections such as wounds, abscesses, cellulitis, superficial/juvenile and deep pyoderma due to susceptible strains of the following organisms: β-lactamase-producing *Staphylococcus aureus*, non-β-lactamase-producing *Staphylococcus aureus, Staphylococcus spp., Streptococcus spp.,* and *E. coli.*

Periodontal infections due to susceptible strains of both aerobic and anaerobic bacteria. Amoxicillin and clavulanate potassium for oral suspension has been shown to be clinically effective for treating cases of canine periodontal disease.

Cats: Skin and soft tissue infections such as wounds, abscesses, and cellulitis/dermatitis due to susceptible strains of the following organisms: β-lactamase-producing *Staphylococcus aureus*, non-β-lactamase-producing *Staphylococcus aureus, Staphylococcus spp., Streptococcus spp., E. coli, Pasteurella multocida*, and *Pasteurella spp.*

Urinary tract infections (cystitis) due to susceptible strains of *E. coli.*

Therapy may be initiated with Amoxicillin and Clavulanate Potassium for Oral Suspension prior to obtaining results from bacteriological and susceptibility studies.

A culture should be obtained prior to treatment to determine susceptibility of the organisms to Amoxicillin and Clavulanate Potassium for Oral Suspension. Following determination of susceptibility results and clinical response to medication, therapy may be reevaluated.

CONTRAINDICATIONS: The use of this drug is contraindicated in animals with a history of an allergic reaction to any of the penicillins or cephalosporins.

WARNINGS: Safety of use in pregnant or breeding animals has not been determined. For use in dogs and cats only.

Keep Amoxicillin and Clavulanate Potassium for Oral Suspension in a secure location out of reach of dogs, cats and other animals to prevent accidental ingestion or overdose.

ADVERSE REACTIONS: Amoxicillin and Clavulanate Potassium for Oral Suspension contains a semisynthetic penicillin (amoxicillin) and has the potential for producing allergic reactions.

If an allergic reaction occurs, administer epinephrine and/or steroids.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet, contact Cronus Pharma LLC at 1-844-227-6687. For additional information about adverse experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

DOSAGE AND ADMINISTRATION:
Dogs: The recommended dosage is 6.25 mg/lb (1 mL/10 lb) of body weight twice a day. Skin and soft tissue infections such as abscesses, cellulitis, wounds, superficial/juvenile pyoderma, and periodontal infections should be treated for 5–7 days or for 48 hours after all symptoms have subsided. If no response is seen after 5 days of treatment, therapy should be discontinued and the case reevaluated. Deep pyoderma may require treatment for 21 days; the maximum duration of treatment should not exceed 30 days.

Cats: The recommended dosage is 62.5 mg (1 mL) twice a day. Skin and soft tissue infections such as abscesses and cellulitis/dermatitis should be treated for 5–7 days or 48 hours after all symptoms have subsided, not to exceed 30 days. If no response is seen after 3 days of treatment, therapy should be discontinued and the case reevaluated.

Urinary tract infections may require treatment for 10–14 days or longer. The maximum duration of treatment should not exceed 30 days.

RECONSTITUTION INSTRUCTIONS - ORAL SUSPENSION: Add 14 mL of water to the 15-mL bottle and shake vigorously. Each mL of suspension will contain 50 mg of amoxicillin activity as the trihydrate and 12.5 mg of clavulanic acid activity as the potassium salt.

Note: Any unused portion of the reconstituted suspension must be discarded after 10 days. Refrigeration of the reconstituted suspension is required.

STORAGE CONDITIONS: Do not store dry powder at temperatures above 25°C (77°F).

HOW SUPPLIED: Amoxicillin and Clavulanate Potassium for Oral Suspension drops are supplied in 15-mL bottles containing 50 mg of amoxicillin/12.5 mg of clavulanic acid per mL.

Approved by FDA under ANADA # 200-709
Augmentin® is a trademark owned by **GlaxoSmithKline.**

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816.
Contact No: 1-844-227-6687
(1-844-2-CRONUS)
P1528366
Made in India
Revised: April 2021

TAKE TIME. OBSERVE LABEL DIRECTIONS.

AMOXICILLIN AND CLAVULANATE POTASSIUM TABLETS

For use in dogs and cats

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Amoxicillin and Clavulanate Potassium Tablets are an orally administered formulation comprised of the broad-spectrum antibiotic amoxicillin trihydrate and the ß-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid).

Amoxicillin trihydrate is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram-negative, aerobic and anaerobic microorganisms. It does not resist destruction by ß-lactamases; therefore, it is not effective against ß-lactamase producing bacteria. Chemically, it is D (-)-ß-amino-p-hydroxybenzyl penicillin trihydrate.

Clavulanic acid, an inhibitor of ß-lactamase enzymes, is produced by the fermentation of Streptomyces clavuligerus. Clavulanic acid by itself has only weak antibacterial activity. Chemically, clavulanate potassium is potassium z-(3R,5R)-2-ß-hydroxyethylidene clavam-3-carboxylate.

ACTIONS: Amoxicillin and Clavulanate Potassium Tablets are stable in the presence of gastric acid and are not significantly influenced by gastric or intestinal contents. The 2 components are rapidly absorbed resulting in amoxicillin and clavulanic acid concentrations in serum, urine, and tissues similar to those produced when each is administered alone.

Amoxicillin and clavulanic acid diffuse readily into most body tissues and fluids with the exception of brain and spinal fluid, which amoxicillin penetrates adequately when meninges are inflamed. Most of the amoxicillin is excreted unchanged in the urine. Clavulanic acid's penetration into spinal fluid is unknown at this time. Approximately 15% of the administered dose of clavulanic acid is excreted in the urine within the first 6 hours.

Amoxicillin and Clavulanate Potassium Tablets combine the distinctive properties of a broad-spectrum antibiotic and a ß-lactamase inhibitor to effectively extend the antibacterial spectrum of amoxicillin to include ß-lactamase producing as well as non-ß-lactamase-producing aerobic and anaerobic organisms.

MICROBIOLOGY: Amoxicillin is bactericidal in action and acts through the inhibition of biosynthesis of cell wall mucopeptide of susceptible organisms. The action of clavulanic acid extends the antimicrobial spectrum of amoxicillin to include organisms resistant to amoxicillin and other ß-lactam antibiotics. Amoxicillin/clavulanate has been shown to have a wide range of activity which includes ß-lactamase producing strains of both gram-positive and gram-negative aerobes, facultative anaerobes, and obligate anaerobes. Many strains of the following organisms, including ß-lactamase-producing strains, isolated from veterinary sources, were found to be susceptible to amoxicillin/clavulanate in vitro but the clinical significance of this activity has not been demonstrated for some of these organisms in animals.

Aerobic bacteria, including *Staphylococcus aureus*[1], ß-lactamase producing *Staphylococcus aureus*[1] (penicillin resistant), *Staphylococcus* species[1], *Staphylococcus* epidermidis, *Staphylococcus intermedius*, *Streptococcus faecalis*, *Streptococcus* species[1] , *Corynebacterium pyogenes, Corynebacterium species, Erysipelothrix rhusiopathiae, 1 Bordetella bronchiseptica, Escherichia coli*[1], *Proteus mirabilis, Proteus species, Enterobacter species, Klebsiella pneumoniae, Salmonella dublin, Salmonella typhimurium, Pasteurella multocida, Pasteurella haemolytica, Pasteurella* species[1]

[1] The susceptibility of these organisms has also been demonstrated in in vivo studies.

Studies have demonstrated that both aerobic and anaerobic flora are isolated from gingival cultures of dogs with clinical evidence of peridontal disease. Both gram-positive and gram-negative aerobic and anaerobic subgingival isolates indicate sensitivity to amoxicillin/clavulanic acid during antimicrobial susceptibility testing.

SUSCEPTIBILITY TEST: The recommended quantitative disc susceptibility method (FEDERAL REGISTER 37:20527-29; Bauer AW, Kirby WMM, Sherris JC, et al: Antibiotic susceptibility testing by standardized single disc method. Am J Clin Path 45:493, 1966) utilized 30 mcg Augmentin® (AMC) discs for estimating the susceptibility of bacteria to amoxicillin and clavulanate potassium tablets.

INDICATIONS: Amoxicillin and Clavulanate Potassium Tablets are indicated in the treatment of:

Dogs: Skin and soft tissue infections such as wounds, abscesses, cellulitis, superficial/juvenile and deep pyoderma due to susceptible strains of the following organisms: ß-lactamase-producing *Staphylococcus aureus*, non- ß-lactamase-producing *Staphylococcus aureus, Staphylococcus* spp., *Streptococcus* spp., and E. *coli.*

Periodontal infections due to susceptible strains of both aerobic and anaerobic bacteria. Amoxicillin and Clavulanate Potassium Tablets have been shown to be clinically effective for treating cases of canine periodontal disease.

Cats: Skin and soft tissue infections such as wounds, abscesses, and cellulitis/dermatitis due to susceptible strains of the following organisms: ß-lactamase-producing *Staphylococcus aureus*, non-ß-lactamase-producing *Staphylococcus aureus*, *Staphylococcus* spp., *Streptococcus* spp., *E. coli*, and *Pasteurella spp.* Urinary tract infections (cystitis) due to susceptible strains of E. *coli.*

Therapy may be initiated with Amoxicillin and Clavulanate Potassium Tablets prior to obtaining results from bacteriological and susceptibility studies. A culture should be obtained prior to treatment to determine susceptibility of the organisms to Amoxicillin and Clavulanate Potassium Tablets. Following determination of susceptibility results and clinical response to medication, therapy may be reevaluated.

CONTRAINDICATIONS: The use of this drug is contraindicated in animals with a history of an allergic reaction to any of the penicillins or cephalosporins.

WARNINGS: Safety of use in pregnant or breeding animals has not been determined. Store at controlled room temperature, 68-77°F (20-25°C).

Do not remove from foil strip until ready to use
ADVERSE REACTIONS: Amoxicillin and Clavulanate Potassium Tablets contain a semisynthetic penicillin (amoxicillin) and has the potential for producing allergic reactions. If an allergic reaction occurs, administer epinephrine and/or steroids.

Post-Approval Experience (July, 2017):
The following adverse events are based on the post-approval adverse drug experience reporting. Not all adverse events are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a casual relationship to product exposure using these data. The following adverse events reported for dogs and cats are listed in decreasing order of reporting frequency for amoxicillin and clavulanate potassium tablets: Anorexia, lethargy, vomiting and diarrhea. To report suspected adverse events, for technical assistance or to obtain a copy of the Safety Data Sheet, contact Cronus Pharma LLC at 1-844-227- 6687 (1-844-2-CRONUS). For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

DOSAGE AND ADMINISTRATION:
Dogs: The recommended dosage is 6.25 mg/lb of body weight twice a day.

Skin and soft tissue infections such as abscesses, cellulitis, wounds, superficial/juvenile pyoderma, and periodontal infections should be treated for 5-7 days or for 48 hours after all symptoms have subsided.

If no response is seen after 5 days of treatment, therapy should be discontinued and the case reevaluated.

Deep pyoderma may require treatment for 21 days; the maximum duration of treatment should not exceed 30 days.

Cats: The recommended dosage is 62.5 mg twice a day.

Skin and soft tissue infections such as abscesses and cellulitis/dermatitis should be treated for 5-7 days or for 48 hours after all symptoms have subsided, not to exceed 30 days. If no response is seen after 3 days of treatment, therapy should be discontinued and the case reevaluated. Urinary tract infections may require treatment for 10-14 days or longer. The maximum duration of treatment should not exceed 30 days.

HOW SUPPLIED: Amoxicillin and Clavulanate Potassium Tablets in the following strengths are supplied in strip packs. Each carton holds 15 strips with 14 tablets per strip (210 tablets per carton).

Each 62.5-mg tablet contains amoxicillin trihydrate equivalent to 50 mg of amoxicillin activity and 12.5 mg of clavulanic acid as the potassium salt. For use in dogs and cats.

Each 125-mg tablet contains amoxicillin trihydrate equivalent to 100 mg of amoxicillin activity and 25 mg of clavulanic acid as the potassium salt.For use in dogs only.

Each 250-mg tablet contains amoxicillin trihydrate equivalent to 200 mg of amoxicillin activity and 50 mg of clavulanic acid as the potassium salt.For use in dogs only.

Each 375-mg tablet contains amoxicillin trihydrate equivalent to 300 mg of amoxicillin activity and 75 mg of clavulanic acid as the potassium salt.For use in dogs only.

Dispense according to recommendations outlined in Dosage and Administration section.
Augmentin is a trademark owned by GlaxoSmithKline.
Approved by FDA under ANADA # 200-702

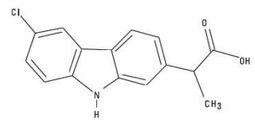
Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816.
Contact No: 1-844-227-6687
(1-844-2-CRONUS)
P1517555
Made in India
Revised: March 2021

CAROFENVET™ (CARPROFEN) STERILE INJECTABLE SOLUTION 50 MG/ML

Non-steroidal anti-inflammatory drug
For subcutaneous use in dogs only.

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Carofenvet™ Injectable is a sterile solution containing carprofen, a non-steroidal anti-inflammatory drug (NSAID) of the propionic acid class that includes ibuprofen, naproxen, and ketoprofen. Carprofen is the non-proprietary designation for a substituted carbazole, 6-chloro-α-methyl-9H-carbazole-2-acetic acid. The empirical formula is $C_{15}H_{12}ClNO_2$ and molecular weight 273.72. The chemical structure of carprofen is:



Each mL of Carofenvet™ Injectable contains 50.0 mg carprofen, 30.0 mg arginine, 88.5 mg glycocholic acid, 169.0 mg lecithin, 10.0 mg benzyl alcohol, 6.17 mg sodium hydroxide, with additional sodium hydroxide and hydrochloric acid as needed to adjust pH, and water for injection.

CLINICAL PHARMACOLOGY: Carprofen is a non-narcotic, non-steroidal anti-inflammatory agent with characteristic analgesic and antipyretic activity approximately equipotent to indomethacin in animal models.[1]

The mechanism of action of carprofen, like that of other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase activity. Two unique cyclooxygenases have been described in mammals.[2] The constitutive cyclooxygenase, COX-1, synthesizes prostaglandins necessary for normal gastrointestinal and renal function. The inducible cyclooxygenase, COX-2, generates prostaglandins involved in inflammation. Inhibition of COX-1 is thought to be associated with gastrointestinal and renal toxicity while inhibition of COX-2 provides anti-inflammatory activity. The specificity of a particular NSAID for COX-2 versus COX-1 may vary from species to species.[3] In an in vitro study using canine cell cultures, carprofen demonstrated selective inhibition of COX-2 versus COX-1.[4] Clinical relevance of these data has not been shown. Carprofen has also been shown to inhibit the release of several prostaglandins in two inflammatory cell systems: rat polymorphonuclear leukocytes (PMN) and human rheumatoid synovial cells, indicating inhibition of acute (PMN system) and chronic (synovial cell system) inflammatory reactions.[1]

Several studies have demonstrated that carprofen has modulatory effects on both humoral and cellular immune responses.[5–9] Data also indicate that carprofen inhibits the production of osteoclast-activating factor (OAF), PGE_1, and PGE_2 by its inhibitory effects on prostaglandin biosynthesis.[1]

Based upon comparison with data obtained from intravenous administration, carprofen is rapidly and nearly completely absorbed (more than 90% bioavailable) when administered orally.[10] Peak blood plasma concentrations are achieved in 1–3 hours after oral administration of 1, 5, and 25 mg/kg to dogs. The mean terminal half-life of carprofen is approximately 8 hours (range 4.5–9.8 hours) after single oral doses varying from 1–35 mg/kg of body weight. After a 100 mg single intravenous bolus dose, the mean elimination half-life was approximately 11.7 hours in the dog. Carprofen is more than 99% bound to plasma protein and exhibits a very small volume of distribution. Comparison of a single 25 mg dose in Beagle dogs after subcutaneous and oral administration demonstrated that the dorsoscapular subcutaneous administration results in a slower rate of drug input (as reflected by mean peak observed concentrations) but comparable total drug absorption within a 12 hour dosing interval (as reflected by area under the curve from hours zero to 12 postdose). Carprofen is eliminated in the dog primarily by biotransformation in the liver followed by rapid excretion of the resulting metabolites (the ester glucuronide of carprofen and the ether glucuronides of 2 phenolic metabolites, 7-hydroxy carprofen and 8-hydroxy carprofen) in the feces (70–80%) and urine (10–20%). Some enterohepatic circulation of the drug is observed.

INDICATIONS: Carofenvet™ is indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

CONTRAINDICATIONS: Carofenvet™ should not be used in dogs exhibiting previous hypersensitivity to carprofen.

WARNINGS: Keep out of reach of children. Not for human use. Consult a physician in cases of accidental human exposure. **For use in dogs only**. Do not use in cats.

All dogs should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests to establish hematological and serum biochemical baseline data prior to, and periodically during, administration of any NSAID should be considered. **Owners should be advised to observe for signs of potential drug toxicity (see Adverse Reactions, Animal Safety and Post-Approval Experience).**

PRECAUTIONS: As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Effects may result from decreased prostaglandin production and inhibition of the enzyme cyclooxygenase which is responsible for the formation of prostaglandins from arachidonic acid.[11–14] When NSAIDs inhibit prostaglandins that cause inflammation they may also inhibit those prostaglandins which maintain normal homeostatic function. These anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease more often than in healthy patients.[12,14] NSAID therapy could unmask occult disease which has previously been undiagnosed due to the absence of apparent clinical signs. Patients with underlying renal disease for example, may experience exacerbation or decompensation of their renal disease while on NSAID therapy.[11–14] The use of parenteral fluids during surgery should be considered to reduce the potential risk of renal complications when using NSAIDs perioperatively.

Carprofen is an NSAID, and as with others in that class, adverse reactions may occur with its use. The most frequently reported effects have been gastrointestinal signs. Events involving suspected renal, hematologic, neurologic, dermatologic, and hepatic effects have also been reported. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be approached cautiously, with appropriate monitoring. Concomitant use of Carofenvet™ with other anti-inflammatory drugs, such as other NSAIDs or corticosteroids, should be avoided because of the potential increase of adverse reactions, including gastrointestinal ulcerations and/or perforations.

Sensitivity to drug-associated adverse reactions varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Carofenvet™ treatment was not associated with renal toxicity or gastrointestinal ulceration in well-controlled safety studies of up to ten times the dose in healthy dogs. As with any parenterally injected product, good hygienic procedures should be used when administering Carofenvet™ Injectable. It is suggested to use different sites for additional injections.

Carofenvet™ is not recommended for use in dogs with bleeding disorders (e.g., Von Willebrand's disease), as safety has not been established in dogs with these disorders. The safe use of Carofenvet™ in animals less than 6 weeks of age, pregnant dogs, dogs used for breeding purposes, or in lactating bitches has not been established. Safety has not been established for IV or IM administration. Studies to determine the activity of Carofenvet™ when administered concomitantly with other protein-bound or similarly metabolized drugs have not been conducted. Drug compatibility should be monitored closely in patients requiring additional therapy. Such drugs commonly used include cardiac, anticonvulsant and behavioral medications. It has been suggested that treatment with carprofen may reduce the level of inhalant anesthetics needed.15 If additional pain medication is warranted after administration of the total daily dose of Carofenvet™, alternative analgesia should be considered. The use of another NSAID is not recommended. Consider appropriate washout times when switching from one NSAID to another or when switching from corticosteroid use to NSAID use.

INFORMATION FOR DOG OWNERS: Carofenvet™, like other drugs of its class, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with drug intolerance. Adverse reactions may include decreased appetite, vomiting, diarrhea, dark or tarry stools, increased water consumption, increased urination, pale gums due to anemia, yellowing of gums, skin or white of the eye due to jaundice, lethargy, incoordination, seizure, or behavioral changes. **Serious adverse reactions associated with this drug class can occur without warning and in rare situations result in death (see Adverse Reactions). Owners should be advised to discontinue Carofenvet™ therapy and contact their veterinarian immediately if signs of intolerance are observed.** The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized, the drug is withdrawn, and veterinary care, if appropriate, is initiated. Owners should be advised of the importance of periodic follow up for all dogs during administration of any NSAID.

ADVERSE REACTIONS: During investigational studies for the caplet formulation, no clinically significant adverse reactions were reported. Some clinical signs were observed during field studies (n=297) which were similar for carprofen- and placebo-treated dogs. Incidences of the following were observed in both groups:

vomiting (4%), diarrhea (4%), changes in appetite (3%), lethargy (1.4%), behavioral changes (1%), and constipation (0.3%). The product vehicle served as control. There were no serious adverse events reported during clinical field studies with once daily oral administration of 2 mg/lb. The following categories of abnormal health observations were reported. The product vehicle served as control.

Percentage of Dogs with Abnormal Health Observations Reported in Clinical Field Study (2 mg/lb once daily)

Observation	Carprofen Injectable (n=129)	Placebo (n=132)
Inappetence	1.6	1.5
Vomiting	3.1	3.8
Diarrhea/Soft stool	3.1	4.5
Behavior change	0.8	0.8
Dermatitis	0.8	0.8
PU/PD	0.8	—
SAP increase	7.8	8.3
ALT increase	5.4	4.5
AST increase	2.3	0.8
BUN increase	3.1	1.5
Bilirubinuria	16.3	12.1
Ketonuria	14.7	9.1

Clinical pathology parameters listed represent reports of increases from pre-treatment values; the use of clinical judgement is necessary to determine clinical relevance (refers also to table below).

There were no serious adverse events reported during clinical field studies for the injectable formulation. The following categories of abnormal health observations were reported. Saline served as placebo control.

Percentage of Dogs with Abnormal Health Observations Reported in Clinical Field Studies with the Injectable

Observation*	Carprofen Injectable (n=168)	Placebo (n=163)
Vomiting	10.1	9.2
Diarrhea/soft stool	2.4	3.7
Dermatitis	0.6	1.2
Dysrhythmia	0.6	0.6
Swelling	0	1.2
Dehiscence	1.2	0
WBC increase	13.7	6.7

* A single dog may have experienced more than one occurrence of an event.

Post-Approval Experience: Although not all adverse reactions are reported, the following adverse reactions are based on voluntary post-approval adverse drug experience reporting. The categories of adverse reactions are listed by body system.

Gastrointestinal: *Vomiting, diarrhea, constipation, inappetence, melena, hematemesis, gastrointestinal ulceration, gastrointestinal bleeding, pancreatitis.*

Hepatic: *Inappetence, vomiting, jaundice, acute hepatic toxicity, hepatic enzyme elevation, abnormal liver function test(s), hyperbilirubinemia, bilirubinuria, hypoalbuminemia. Approximately one-fourth of hepatic reports were in Labrador Retrievers.*

Neurologic: *Ataxia, paresis, paralysis, seizures, vestibular signs, disorientation.*

Urinary: *Hematuria, polyuria, polydipsia, urinary incontinence, urinary tract infection, azotemia, acute renal failure, tubular abnormalities including acute tubular necrosis, renal tubular acidosis, glucosuria.*

Behavioral: *Sedation, lethargy, hyperactivity, restlessness, aggressiveness.*

Hematologic: *Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, blood loss anemia, epistaxis.*

Dermatologic: *Pruritus, increased shedding, alopecia, pyotraumatic moist dermatitis (hot spots), necrotizing panniculitis/vasculitis, ventral ecchymosis.*

In rare situations, injection site reactions including necrosis, abscess and seroma formation, and granulomas have been reported with the injectable formulation.

Immunologic or hypersensitivity: *Facial swelling, hives, erythema.*

In rare situations, death has been associated with some of the adverse reactions listed above.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet, contact Cronus Pharma LLC at 1-844-227-6687 or 1-844-2-CRONUS. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

DOSAGE AND ADMINISTRATION: Carefully consider the potential benefits and risks of Carofenvet™ and other treatment options before deciding to use Carofenvet™. Use the lowest effective dose for the shortest duration consistent with individual response. The recommended dosage for subcutaneous administration to dogs is 2 mg/lb (4.4 mg/kg) of body weight daily. The total daily dose may be administered as either 2 mg/lb of body weight once daily or divided and administered as 1 mg/lb (2.2 mg/kg) twice daily. For control of postoperative pain, administer approximately 2 hours before the procedure.

EFFECTIVENESS: Confirmation of the effectiveness of carprofen for the relief of pain and inflammation associated with osteoarthritis, and for the control of postoperative pain associated with soft tissue and orthopedic surgeries was demonstrated in 7 placebo-controlled, masked studies examining the anti-inflammatory and analgesic effectiveness of carprofen caplets and injectable in various breeds of dogs.

Separate placebo-controlled, masked, multicenter field studies confirmed the anti-inflammatory and analgesic effectiveness of carprofen caplets when dosed at 2 mg/lb once daily or when divided and administered at 1 mg/lb twice daily. In these two field studies, dogs diagnosed with osteoarthritis showed statistically significant overall improvement based on lameness evaluations by the veterinarian and owner observations when administered carprofen at labeled doses.

Based upon the blood level comparison between subcutaneous and oral administration, carprofen effectiveness for osteoarthritis after dorsoscapular subcutaneous and oral administration should be similar, although there may be a slight delay in the onset of relief after subcutaneous injection.

Separate placebo-controlled, masked, multicenter field studies confirmed the effectiveness of carprofen injectable for the control of postoperative pain when dosed at 2 mg/lb once daily in various breeds of dogs. In these studies, dogs presented for ovariohysterectomy, cruciate repair and aural surgeries were administered carprofen preoperatively and for a maximum of 3 days (soft tissue) or 4 days (orthopedic) postoperatively. In general, dogs administered carprofen showed statistically significant improvement in pain scores compared to controls.

ANIMAL SAFETY: Laboratory studies in unanesthetized dogs and clinical field studies have demonstrated that carprofen is well tolerated in dogs after oral and subcutaneous administration.

In target animal safety studies, carprofen was administered orally to healthy Beagle dogs at 1, 3, and 5 mg/lb twice daily (1, 3 and 5 times the recommended total daily dose) for 42 consecutive days with no significant adverse reactions. Serum albumin for a single female dog receiving 5 mg/lb twice daily decreased to 2.1 g/dL after 2 weeks of treatment, returned to the pre-treatment value (2.6 g/dL) after 4 weeks of treatment, and was 2.3 g/dL at the final 6-week evaluation. Over the 6-week treatment period, black or bloody stools were observed in 1 dog (1 incident) treated with 1 mg/lb twice daily and in 1 dog (2 incidents) treated with 3 mg/lb twice daily. Redness of the colonic mucosa was observed in 1 male that received 3 mg/lb twice daily.

Two of 8 dogs receiving 10 mg/lb orally twice daily (10 times the recommended total daily dose) for 14 days exhibited hypoalbuminemia. The mean albumin level in the dogs receiving this dose was lower (2.38 g/dL) than each of 2 placebo control groups (2.88 and 2.93 g/dL, respectively). Three incidents of black or bloody stool were observed in 1 dog. Five of 8 dogs exhibited reddened areas of duodenal mucosa on gross pathologic examination. Histologic examination of these areas revealed no evidence of ulceration, but did show minimal congestion of the lamina propria in 2 of the 5 dogs.

In separate safety studies lasting 13 and 52 weeks, respectively, dogs were administered orally up to 11.4 mg/lb/day (5.7 times the recommended total daily dose of 2 mg/lb) of carprofen. In both studies, the drug was well tolerated clinically by all of the animals. No gross or histologic changes were seen in any of the treated animals. In both studies, dogs receiving the highest doses had average increases in serum L-alanine aminotransferase (ALT) of approximately 20 IU.

In the 52 week study, minor dermatologic changes occurred in dogs in each of the treatment groups but not in the control dogs. The changes were described as slight redness or rash and were diagnosed as non-specific dermatitis. The possibility exists that these mild lesions were treatment related, but no dose relationship was observed.

Clinical field studies were conducted with 549 dogs of different breeds at the recommended oral doses for 14 days (297 dogs were included in a study evaluating 1 mg/lb twice daily and 252 dogs were included in a separate study evaluating 2 mg/lb once daily). In both studies the drug was clinically well tolerated and the incidence of clinical adverse reactions for carprofen-treated animals was no higher than placebo-treated animals (placebo contained inactive ingredients found in carprofen caplets). For animals receiving 1 mg/lb twice daily, the mean post-treatment serum ALT values were 11 IU greater and 9 IU less than pre-treatment values for dogs receiving carprofen caplets and placebo, respectively. Differences were not statistically significant. For animals receiving 2 mg/lb once daily, the mean post-treatment serum ALT values were 4.5 IU greater and 0.9 IU less than pre-treatment values for dogs receiving carprofen caplets and placebo, respectively. In the latter study, 3 carprofen-treated dogs developed a 3-fold or greater increase in (ALT) and/or (AST) during the course of therapy. One placebo-treated dog had a greater than 2-fold increase in ALT. None of these animals showed clinical signs associated with the laboratory value changes. Changes in clinical laboratory values (hematology and clinical chemistry) were not considered clinically significant. The 1 mg/lb twice daily course of therapy was repeated as needed at 2-week intervals in 244 dogs, some for as long as 5 years.

Clinical field studies were conducted on 331 dogs undergoing orthopedic or soft tissue surgery. Dogs were administered 2 mg/lb of carprofen subcutaneously two hours prior to surgery and once daily thereafter, as needed, for 2 days (soft tissue surgery) or 3 days (orthopedic surgery). Carprofen was well tolerated when used in conjunction with a variety of anesthetic-related drugs. The type and severity of abnormal health observations in carprofen- and placebo-treated animals were approximately equal and few in number (see Adverse Reactions). The most frequent abnormal health observation was vomiting and was observed at approximately the same frequency in carprofen- and placebo-treated animals.

Changes in clinicopathologic indices of hematopoietic, renal, hepatic, and clotting function were not clinically significant. The mean post-treatment serum ALT values were 8.4 IU and 7.0 IU less than pre- treatment values for dogs receiving carprofen and placebo, respectively. The mean post-treatment AST values were 1.5 IU and 0.7 IU greater for dogs receiving carprofen and placebo, respectively.

Swelling and warmth were associated with the injection site after subcutaneous administration of carprofen injectable. These findings were not clinically significant. Long term use of the injectable has not been studied.

STORAGE: Store under refrigeration 2°- 8°C (36°–46°F). Once broached, product may be stored at temperatures up to 25°C (77°F) for 56 days.

HOW SUPPLIED: Carofenvet™ Injectable is supplied in 20-mL and 50-mL, amber, glass, sterile, multi-dose vials.

REFERENCES:

1. Baruth H, *et al:* In Anti-Inflammatory and Anti-Rheumatic Drugs, Vol. II, Newer Anti-Inflammatory Drugs, Rainsford KD, ed. CRC Press, Boca Raton, pp. 33–47, 1986.
2. Vane JR, Botting RM: Mechanism of action of anti-inflammatory drugs. *Scand J Rheumatol* 25:102, pp. 9–21.
3. Grossman CJ, Wiseman J, Lucas FS, *et al:* Inhibition of constitutive and inducible cyclooxygenase activity in human platelets and mononuclear cells by NSAIDs and COX-2 inhibitors. *Inflammation Research* 44:253–257, 1995.
4. Ricketts AP, Lundy KM, Seibel SB: Evaluation of selective inhibition of canine cyclooxgenase 1 and 2 by carprofen and other nonsteroidal anti-inflammatory drugs. *Am J Vet Res* 59:11, pp. 1441– 1446, November 1998.
5. Ceuppens JL, *et al:* Non-steroidal anti-inflammatory agents inhibit the synthesis of IgM rheumatoid factor *in vitro*. Lancet 1:528, 1982.
6. Ceuppens JL, *et al:* Endogenous prostaglandin E2 enhances polyclonal immunoglobulin production by ionically inhibiting T suppressor cell activity. *Cell Immunol* 70:41, 1982.
7. Schleimer RP, *et al*: The effects of prostaglandin synthesis inhibition on the immune response. *Immunopharmacology* 3:205, 1981.
8. Leung KH, *et al*: Modulation of the development of cell mediated immunity: possible roles of the products of cyclooxgenase and lipoxygenase pathways of arachidonic acid metabolism. *Int J Immunopharmacology* 4:195, 1982.
9. Veit BC: Immunoregulatory activity of cultured-induced suppressor macrophages. Cell Immunol 72:14, 1982.
10. Schmitt M, et al: Biopharmaceutical evaluation of carprofen following single intravenous, oral, and rectal doses in dogs. *Biopharm Drug Dispos* 11(7):585–94, 1990.
11. Kore AM: Toxicology of nonsteroidal anti-inflammatory drugs. Veterinary Clinics of North America, *Small Animal Practice* 20, March 1990.
12. Binns SH: Pathogenesis and pathophysiology of ischemic injury in cases of acute renal failure. *Compend for Cont Ed* 16:1, January 1994.
13. Boothe DM: Prostaglandins: Physiology and clinical implications. *Compend for Cont Ed* 6:11, November 1984.
14. Rubin SI: Nonsteroidal anti-inflammatory drugs, prostaglandins, and the kidney. *JAVMA* 188:9, May 1986.
15. Ko CH, Lange DN, Mandsager RE, et al: Effects of butorphanol and carprofen on the minimal alveolar concentration of isoflurane in dogs. *JAVMA* 217:1025–1028, 2000.

Approved by FDA under ANADA # 200-762

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816.
Contact No: 1-844-227-6687
(1-844-2-CRONUS)

Made in India

Revised: January 2024

PC046-00

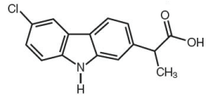
TAKE TIME.
OBSERVE LABEL
DIRECTIONS.

CARPROFEN CHEWABLE TABLETS

Non-steroidal anti-inflammatory drug
For oral use in dogs only

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Carprofen Chewable Tablets (carprofen) are a non-steroidal anti-inflammatory drug (NSAID) of the v acid class that includes ibuprofen, naproxen, and ketoprofen. Carprofen is the nonproprietary designation for a substituted carbazole, 6-chloro-α-methyl-9H-carbazole-2-acetic acid. The empirical formula is $C_{15}H_{12}ClNO_2$ and the molecular weight 273.72. The chemical structure of carprofen is:



Carprofen is a white, crystalline compound. It is freely soluble in ethanol, but practically insoluble in water at 25°C.

CLINICAL PHARMACOLOGY: Carprofen is a non-narcotic, non-steroidal anti-inflammatory agent with characteristic analgesic and antipyretic activity approximately equipotent to indomethacin in animal models[1].

The mechanism of action of carprofen, like that of other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase activity. Two unique cyclooxygenases have been described in mammals[2]. The constitutive cyclooxygenase, COX-1, synthesizes prostaglandins necessary for normal gastrointestinal and renal function. The inducible cyclooxygenase, COX-2, generates prostaglandins involved in inflammation. Inhibition of COX-1 is thought to be associated with gastrointestinal and renal toxicity while inhibition of COX-2 provides anti-inflammatory activity. The specificity of a particular NSAID for COX-2 versus COX-1 may vary from species to species[3]. In an *in vitro* study using canine cell cultures, carprofen demonstrated selective inhibition of COX-2 versus COX-1.[4] Clinical relevance of these data has not been shown. Carprofen has also been shown to inhibit the release of several prostaglandins in two inflammatory cell systems: rat polymorphonuclear leukocytes (PMN) and human rheumatoid synovial cells, indicating inhibition of acute (PMN system) and chronic (synovial cell system) inflammatory reactions[1].

Several studies have demonstrated that carprofen has modulatory effects on both humoral and cellular immune responses[5-9]. Data also indicate that carprofen inhibits the production of osteoclast-activating factor (OAF), PGE1 , and PGE_2 by its inhibitory effect in prostaglandin biosynthesis[1] .

Based upon comparison with data obtained from intravenous administration, carprofen is rapidly and nearly completely absorbed (more than 90% bioavailable) when administered orally[10]. Peak blood plasma concentrations are achieved in 1-3 hours after oral administration of 1, 5, and 25 mg/kg to dogs. The mean terminal half-life of carprofen is approximately 8 hours (range 4.5-9.8 hours) after single oral doses varying from 1-35 mg/kg of body weight. After a 100 mg single intravenous bolus dose, the mean elimination half-life was approximately 11.7 hours in the dog. Carprofen is more than 99% bound to plasma protein and exhibits a very small volume of distribution.

Carprofen is eliminated in the dog primarily by biotransformation in the liver followed by rapid excretion of the resulting metabolites (the ester glucuronide of carprofen and the ether glucuronides of 2 phenolic metabolites, 7-hydroxy carprofen and 8-hydroxy carprofen) in the feces (70-80%) and urine (10-20%). Some enterohepatic circulation of the drug is observed.

INDICATIONS: Carprofen Chewable Tablets are indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

CONTRAINDICATIONS: Carprofen Chewable Tablets should not be used in dogs exhibiting previous hypersensitivity to carprofen.

WARNINGS: Keep out of reach of children. Not for human use. Consult a physician in cases of accidental ingestion by humans. **For use in dogs only.** Do not use in cats. All dogs should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests to establish hematological and serum biochemical baseline data prior to, and periodically during, administration of any NSAID should be considered. **Owners should be advised to observe for signs of potential drug toxicity (see Information for Dog Owners, Adverse Reactions, Animal Safety and Post-Approval Experience).**

PRECAUTIONS: As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Effects may result from decreased prostaglandin production and inhibition of the enzyme cyclooxygenase which is responsible for the formation of prostaglandins from arachidonic acid[11-14]. When NSAIDs inhibit prostaglandins that cause inflammation they may also inhibit those prostaglandins which maintain normal homeostatic function. These anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease more often than in healthy patients[12, 14].NSAID therapy could unmask occult disease which has previously been undiagnosed due to the absence of apparent clinical signs. Patients with underlying renal disease for example, may experience exacerbation or decompensation of their renal disease while on NSAID therapy[11-14]. The use of parenteral fluids during surgery should be considered to reduce the potential risk of renal complications when using NSAIDs perioperatively.

Carprofen is an NSAID, and as with others in that class, adverse reactions may occur with its use. The most frequently reported effects have been gastrointestinal signs. Events involving suspected renal, hematologic, neurologic, dermatologic, and hepatic effects have also been reported. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be approached cautiously, with appropriate monitoring. Concomitant use of Carprofen Chewable Tablets with other anti-inflammatory drugs, such as other NSAIDs or corticosteroids, should be avoided because of the potential increase of adverse reactions, including gastrointestinal ulcerations and/or perforations. Sensitivity to drug-associated adverse reactions varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Carprofen treatment was not associated with renal toxicity or gastrointestinal ulceration in well-controlled safety studies of up to ten times the dose in healthy dogs.

Carprofen Chewable Tablets are not recommended for use in dogs with bleeding disorders (e.g., Von Willebrand's disease), as safety has not been established in dogs with these disorders. The safe use of Carprofen Chewable Tablets in animals less than 6 weeks of age, pregnant dogs, dogs used for breeding purposes, or in lactating bitches has not been established. Studies to determine the activity of Carprofen Chewable Tablets when administered concomitantly with other protein-bound or similarly metabolized drugs have not been conducted. Drug compatibility should be monitored closely in patients requiring additional therapy. Such drugs commonly used include cardiac, anticonvulsant and behavioral medications. It has been suggested that treatment with carprofen may reduce the level of inhalant anesthetics needed[15].

If additional pain medication is warranted after administration of the total daily dose of Carprofen Chewable Tablets, alternative analgesia should be considered. The use of another NSAID is not recommended. Consider appropriate washout times when switching from one NSAID to another or when switching from corticosteroids use to NSAID use.

Due to the flavoring contained in Carprofen Chewable Tablets, store out of the reach of dogs and in a secured area. Severe adverse reactions may occur if large quantities of tablets are ingested. If you suspect your dog has consumed Carprofen Chewable Tablets above the labeled dose, please call your veterinarian for immediate assistance and notify Cronus Pharma LLC (1-844-227-6687, 1-844-2-CRONUS).

INFORMATION FOR DOG OWNERS: Carprofen Chewable Tablets, like other drugs of its class, are not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with drug intolerance. Adverse reactions may include decreased appetite, vomiting, diarrhea, dark or tarry stools, increased water consumption, increased urination, pale gums due to anemia, yellowing of gums, skin or white of the eye due to jaundice, lethargy, incoordination, seizure, or behavioral changes. **Serious adverse reactions associated with this drug class can occur without warning and in rare situations result in death (see Adverse Reactions). Owners should be advised to discontinue Carprofen Chewable Tablets therapy and contact their veterinarian immediately if signs of intolerance are observed.** The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized, the drug is withdrawn, and veterinary care, if appropriate, is initiated. Owners should be advised of the importance of periodic follow up for all dogs during administration of any NSAID.

ADVERSE REACTIONS: During investigational studies for the caplet formulation with twice daily administration of 1 mg/lb, no clinically significant adverse reactions were reported. Some clinical signs were observed during field studies (n=297) which were similar for carprofen caplet- and placebo-treated dogs. Incidences of the following were observed in both groups: vomiting (4%), diarrhea (4%), changes in appetite (3%), lethargy (1.4%), behavioral changes (1%), and constipation (0.3%). The product vehicle served as control.
There were no serious adverse events reported during clinical field studies with once daily administration of 2 mg/lb. The following categories of abnormal health observations were reported. The product vehicle served as control.

Percentage of Dogs with Abnormal Health Observations Reported in Clinical Field Study (2mg/lb once daily)		
Observation	**Carprofen (n=129)**	**Placebo (n=132)**
Inappetence	1.6	1.5
Vomiting	3.1	3.8
Diarrhea/Soft stool	3.1	4.5
Behavior change	0.8	0.8
Dermatitis	0.8	0.8
PU/PD	0.8	-
SAP increase	7.8	8.3
ALT increase	5.4	4.5
AST increase	2.3	0.8
BUN increase	3.1	1.5
Bilirubinuria	16.3	12.1
Ketonuria	14.7	9.1

Clinical pathology parameters listed represent reports of increases from pre-treatment values; medical judgment is necessary to determine clinical relevance. During investigational studies of surgical pain for the caplet formulation, no clinically significant adverse reactions were reported. The product vehicle served as control.

During investigational studies for the chewable tablet formulation, gastrointestinal signs were observed in some dogs. These signs included vomiting and soft stools.

Percentage of Dogs with Abnormal Health Observations Reported in Surgical Pain Field Studies with Caplets (2 mg/lb once daily)		
Observation*	**Carprofen (n=148)**	**Placebo (n=149)**
Vomiting	10.1	13.4
Diarrhea/Soft stool	6.1	6.0
Ocular disease	2.7	0
Inappetence	1.4	0
Dermatitis/Skin lesion	2.0	1.3
Dysrhythmia	0.7	0
Apnea	1.4	0
Oral/Periodontal disease	1.4	0
Pyrexia	0.7	1.3
Urinary tract disease	1.4	1.3
Wound drainage	1.4	0
*A single dog may have experienced more than one occurrence of an event		

POST-APPROVAL EXPERIENCE: Although not all adverse reactions are reported, the following adverse reactions are based on voluntary post-approval adverse drug experience reporting. The categories of adverse reactions are listed in decreasing order of frequency by body system.

Gastrointestinal: *Vomiting, diarrhea, constipation, inappetence, melena, hematemesis, gastrointestinal ulceration, gastrointestinal bleeding, pancreatitis.*

Hepatic: *Inappetence, vomiting, jaundice, acute hepatic toxicity, hepatic enzyme elevation, abnormal liver function test(s), hyperbilirubinemia, bilirubinuria, hypoalbuminemia Approximately one-fourth of hepatic reports were in Labrador Retrievers.*

Neurologic: *Ataxia, paresis, paralysis, seizures, vestibular signs, disorientation.*

Urinary: *Hematuria, polyuria, polydipsia, urinary incontinence, urinary tract infection, azotemia, acute renal failure, tubular abnormalities including acute tubular necrosis, renal tubular acidosis, glucosuria.*

Behavioral: *Sedation, lethargy, hyperactivity, restlessness, aggressiveness.*

Hematologic: *Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, blood loss anemia, epistaxis.*

Dermatologic: *Pruritus, increased shedding, alopecia, pyotraumatic moist dermatitis (hot spots), necrotizing panniculitis/vasculitis, ventral ecchymosis.*

Immunologic or hypersensitivity: *Facial swelling, hives, erythema.*

In rare situations, death has been associated with some of the adverse reactions listed above.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet, contact Cronus Pharma LLC at 1-844-227-6687 and 1-844-2-CRONUS. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

DOSAGE AND ADMINISTRATION: Always provide Client Information Sheet with prescription. Carefully consider the potential benefits and risk of Carprofen Chewable Tablets and other treatment options before deciding to use Carprofen Chewable Tablets. Use the lowest effective dose for the shortest duration consistent with individual response. The recommended dosage for oral administration to dogs is 2 mg/lb of body weight daily. The total daily dose may be administered as 2 mg/lb of body weight once daily or divided and administered as 1 mg/lb twice daily. For the control of postoperative pain, administer approximately 2 hours before the procedure. Carprofen Chewable Tablets are scored and dosage should be calculated in half-tablet increments. Tablets can be halved by placing the tablet on a hard surface and pressing down on both sides of the score. Carprofen Chewable Tablets may be fed by hand or placed in food. Care should be taken to ensure that the dog consumes the complete dose. Half-tablets should be used within 90 days.

EFFECTIVENESS: Confirmation of the effectiveness of carprofen for the relief of pain and inflammation associated with osteoarthritis, and for the control of postoperative pain associated with soft tissue and orthopedic surgeries, was demonstrated in 5 placebo-controlled, masked studies examining the anti-inflammatory and analgesic effectiveness of carprofen caplets in various breeds of dogs.

Separate placebo-controlled, masked, multicenter field studies confirmed the anti-inflammatory and analgesic effectiveness of carprofen caplets when dosed at 2 mg/lb once daily or when divided and administered at 1 mg/lb twice daily. In these 2 field studies, dogs diagnosed with osteoarthritis showed statistically significant overall improvement based on lameness evaluations by the veterinarian and owner observations when administered carprofen at labeled doses.

Separate placebo-controlled, masked, multicenter field studies confirmed the effectiveness of carprofen caplets for the control of postoperative pain when dosed at 2 mg/lb once daily in various breeds of dogs. In these studies, dogs presented for ovariohysterectomy, cruciate repair and aural surgeries were administered carprofen preoperatively and for a maximum of 3 days (soft tissue) or 4 days (orthopedic) postoperatively. In general, dogs administered carprofen showed statistically significant reduction in pain scores compared to controls.

ANIMAL SAFETY: Laboratory studies in unanesthetized dogs and clinical field studies have demonstrated that carprofen is well tolerated in dogs after oral administration.

In target animal safety studies, carprofen was administered orally to healthy Beagle dogs at 1, 3, and 5 mg/lb twice daily (1, 3 and 5 times the recommended total daily dose) for 42 consecutive days with no significant adverse reactions. Serum albumin for a single female dog receiving 5 mg/lb twice daily decreased to 2.1 g/dl after 2 weeks of treatment, returned to the pre-treatment value (2.6 g/dL) after 4 weeks of treatment, and was 2.3 g/dL at the final 6-week evaluation. Over the 6-week treatment period, black or bloody stools were observed in 1 dog (1 incident) treated with 1 mg/lb twice daily and in 1 dog (2 incidents) treated with 3 mg/lb twice daily. Redness of the colonic mucosa was observed in 1 male that received 3 mg/lb twice daily.

Two of 8 dogs receiving 10 mg/lb orally twice daily (10 times the recommended total daily dose) for 14 days exhibited hypoalbuminemia. The mean albumin level in the dogs receiving this dose was lower (2.38 g/dL) than each of 2 placebo control groups (2.88 and 2.93 g/dL, respectively). Three incidents of black or bloody stool were observed in 1 dog. Five of 8 dogs exhibited reddened areas of duodenal mucosa on gross pathologic examination. Histologic examination of these areas revealed no evidence of ulceration, but did show minimal congestion of the lamina propria in 2 of the 5 dogs.

In separate safety studies lasting 13 and 52 weeks, respectively, dogs were administered orally up to 11.4 mg/lb/day (5.7 times the recommended total daily dose of 2 mg/lb) of carprofen. In both studies, the drug was well tolerated clinically by all of the animals. No gross or histologic changes were seen in any of the treated animals. In both studies, dogs receiving the highest doses had average increases in serum L-alanine aminotransferase (ALT) of approximately 20 IU.

In the 52-week study, minor dermatologic changes occurred in dogs in each of the treatment groups but not in the control dogs. The changes were described as slight redness or rash and were diagnosed as non-specific dermatitis. The possibility exists that these mild lesions were treatment related, but no dose relationship was observed.

Clinical field studies were conducted with 549 dogs of different breeds at the recommended oral doses for 14 days (297 dogs were included in a study evaluating 1 mg/lb twice daily and 252 dogs were included in a separate study evaluating 2 mg/lb once daily). In both studies the drug was clinically well tolerated and the incidence of clinical adverse reactions for carprofen-treated animals was no higher than placebo-treated animals (placebo contained inactive ingredients found in carprofen). For animals receiving 1 mg/lb twice daily, the mean post-treatment serum ALT values were 11 IU greater and 9 IU less than pre-treatment values for dogs receiving carprofen and placebo, respectively. Differences were not statistically significant. For animals receiving 2 mg/lb once daily, the mean post-treatment serum ALT values were 4.5 IU greater and 0.9 IU less than pre-treatment values for dogs receiving carprofen and placebo, respectively. In the latter study, 3 carprofen-treated dogs developed a 3-fold or greater increase in (ALT) and/or (AST) during the course of therapy. One placebo-treated dog had a greater than 2-fold increase in ALT. None of these animals showed clinical signs associated with laboratory value changes. Changes in clinical laboratory values (hematology and clinical chemistry) were not considered clinically significant. The 1 mg/lb twice daily course of therapy was repeated as needed at 2-week intervals in 244 dogs, some for as long as 5 years.

Clinical field studies were conducted in 297 dogs of different breeds undergoing orthopedic or soft tissue surgery. Dogs were administered 2 mg/lb of carprofen two hours prior to surgery then once daily, as needed for 2 days (soft tissue surgery) or 3 days (orthopedic surgery). Carprofen was well tolerated when used in conjunction with a variety of anesthetic-related drugs. The type and severity of abnormal health observation in carprofen- and placebo-treated animals were approximately equal and few in number (see Adverse Reactions). The most frequent abnormal health observation was vomiting and was observed at approximately the same frequency in carprofen- and placebo-treated animals. Changes in clinicopathologic indices of hematopoietic, renal, hepatic, and clotting function were not clinically significant. The mean post-treatment serum ALT values were 7.3 IU and 2.5 IU less than pre-treatment values for dogs receiving carprofen and placebo, respectively. The mean post-treatment AST values were 3.1 IU less for dogs receiving carprofen and 0.2 IU greater for dogs receiving placebo.

STORAGE: Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F). [See USP controlled room temperature.] Protect from light.

HOW SUPPLIED: Carprofen Chewable Tablets are scored, and contain 50mg, 75 mg, or 100 mg of carprofen per tablet. Each tablet size is packaged in bottles containing 60 or 180 tablets.

REFERENCES:

1. Baruth H, *et al:* In Anti-Inflammatory and Anti-Rheumatic Drugs, Vol. II, Newer Anti Inflammatory Drugs, Rainsford KD, ed. CRC Press, Boca Raton, p. 33, 1986.
2. Vane JR, Botting RM: Mechanism of action of anti-inflammatory drugs. *Scand J Rheumatol* 25:102, pp. 9–21.
3. Grossman CJ, Wiseman J, Lucas FS, *et al:* Inhibition of constitutive and inducible cyclooxygenase activity in human platelets and mononuclear cells by NSAIDs and Cox-2 inhibitors. *Inflammation Research* 44:253–257, 1995.
4. Ricketts AP, Lundy KM, Seibel SB: Evaluation of selective inhibition of canine cyclooxygenase 1 and 2 by carprofen and other nonsteroidal anti-inflammatory drugs. *Am J Vet Res* 59:11, pp. 1441–1446, November 1998.
5. Ceuppens JL, *et al:* Non-steroidal anti-inflammatory agents inhibit the synthesis of IgM rheumatoid factor *in vitro. Lancet* 1:528, 1982.
6. Ceuppens JL, *et al:* Endogenous prostaglandin E_2 enhances polyclonal immunoglobulin production by ionically inhibiting T suppressor cell activity. *Cell Immunol* 70:41, 1982.
7. Schleimer RP, *et al:* The effects of prostaglandin synthesis inhibition on the immune response. *Immunopharmacology* 3:205, 1981.

8. Leung KH, *et al*: Modulation of the development of cell mediated immunity: Possible roles of the products of cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism. I*nt J Immunopharmacology* 4:195, 1982.

9. Veit BC: Immunoregulatory activity of cultured-induced suppressor macrophages. *Cell Immunol* 72:14, 1982.

10. Schmitt M, *et al:* Biopharmaceutical evaluation of carprofen following single intravenous, oral, and rectal doses in dogs. *Biopharm Drug Dispos* 11(7):585, 1990.

11. Kore AM: Toxicology of nonsteroidal anti-inflammatory drugs Veterinary Clinics of North America, *Small Animal Practice* 20, March 1990.

12. Binns SH: Pathogenesis and pathophysiology of ischemic injury in cases of acute renal failure. *Compend for Cont Ed* 16:1, January 1994.

13. Boothe DM: Prostaglandins: Physiology and clinical implications. *Compend for Cont Ed* 6:11, November 1984.

14. Rubin SI: Nonsteroidal anti-inflammatory drugs, prostaglandins, and the kidney. *JAVMA* 188:9, May 1986.

15. Ko CH, Lange DN, Mandsager RE, *et al*: Effects of butorphanol and carprofen on the minimal alveolar concentration of isoflurane in dogs. *JAVMA* 217:1025–1028, 2000.

Approved by FDA under ANADA #200-687

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816.
Contact No: 1-844-227-6687
(1-844-2-CRONUS)

Made in India
PIC02760-00

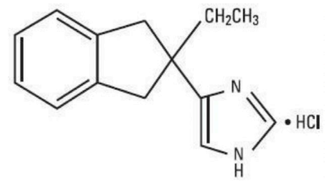
Issued: June 2020

CROPAMEZOLE™ (ATIPAMEZOLE HYDROCHLORIDE)

Sterile Injectable Solution - 5.0 mg/mL
Dexmedetomidine and Medetomidine Reversing Agent
For intramuscular use in dogs only

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Cropamezole™ (atipamezole hydrochloride) is a synthetic α_2-adrenergic antagonist. The chemical name is 4-(2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole hydrochloride. The molecular formula is $C_{14}H_{16}N_2$ • HCl and structural formula is:



Each mL of Cropamezole™ contains 5.0 mg atipamezole hydrochloride, 1.0 mg methylparaben (NF), 8.5 mg sodium chloride (USP), and water for injection (USP).

INDICATIONS: Cropamezole™ is indicated for the reversal of the sedative and analgesic effects of dexmedetomidine hydrochloride, and medetomidine hydrochloride in dogs.

DOSAGE AND ADMINISTRATION: Cropamezole™ is administered intramuscularly (IM) for reversal of sedation and analgesia regardless of the route used for dexmedetomidine hydrochloride or medetomidine hydrochloride. The atipamezole dose for the reversal of IV dexmedetomidine hydrochloride or medetomidine hydrochloride is 3750 mcg/m^2. The atipamezole dose for the reversal of IM dexmedetomidine hydrochloride or medetomidine hydrochloride is 5000 mcg/m^2.

The dosage of Cropamezole™ is calculated based on body surface area. Use the following tables to determine the correct injection volume or the correct Cropamezole™ dosage on the basis of kilograms of body weight.

Note that the mcg/kg dosage decreases as body weight increases.

Table 1: Atipamezole dosing for reversal of IV dexmedetomidine- or medetomidine-induced sedation/analgesia:

Dose table for Cropamezole™ (3750 mcg/m^2) when dexmedetomidine or medetomidine is given IV			
For # lbs	**For # kg**	**dose = mcg/kg**	**Volume = mL Cropamezole™**
4-7	2-3	300	0.1
7-9	3-4	250	0.15
9-11	4-5	230	0.2
11-22	5-10	200	0.3
22-33	10-15	170	0.4
33-44	15-20	150	0.5
44-55	20-25	140	0.6
55-66	25-30	130	0.7
66-81	30-37	120	0.8
81-99	37-45	110	0.9
99-110	45-50	105	1.0
110-132	50-60	100	1.1
132-143	60-65	95	1.2
143-165	65-75	93	1.3
165-176	75-80	91	1.4
>176	>80	90	1.5

Table 2: Atipamezole dosing for reversal of IM dexmedetomidine- or medetomidine-induced sedation/analgesia:

Dose table for Cropamezole™ (5000 mcg/m^2) when dexmedetomidine or medetomidine is given IM			
For # lbs	**For # kg**	**dose = mcg/kg**	**volume = mL Cropamezole™**
4-7	2-3	400	0.15
7-9	3-4	350	0.2
9-11	4-5	300	0.3
11-22	5-10	250	0.4
22-29	10-13	230	0.5
29-33	13-15	210	0.6
33-44	15-20	200	0.7
44-55	20-25	180	0.8
55-66	25-30	170	0.9
66-73	30-33	160	1.0
73-81	33-37	150	1.1
81-99	37-45	145	1.2
99-110	45-50	140	1.3
110-121	50-55	135	1.4
121-132	55-60	130	1.5
132-143	60-65	128	1.6
143-154	65-70	125	1.7
154-176	70-80	123	1.8
>176	>80	120	1.9

CONTRAINDICATIONS: Since atipamezole is always used concomitantly with dexmedetomidine or medetomidine, it should not be used in dogs with the following conditions: cardiac disease, respiratory disorders, liver or kidney diseases, dogs in shock, severely debilitated dogs, or dogs stressed due to extreme heat, cold or fatigue.

Administration of atipamezole is contraindicated in dogs with a known hypersensitivity to the drug.

HUMAN WARNINGS: Not for human use. Keep out of reach of children.

Atipamezole hydrochloride can be absorbed and may cause irritation following direct exposure to skin, eyes, or mouth. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing.

If irritation or other adverse reaction occurs (for example, increased heart rate, tremor, muscle cramps), seek medical attention.

In case of accidental oral exposure or injection, seek medical attention. Caution should be used while handling and using filled syringes.

Users with cardiovascular disease (for example, hypertension or ischemic heart disease) should take special precautions to avoid any exposure to this product.

Note to Physician: This product contains an alpha$_2$-adrenergic antagonist.

PRECAUTIONS:
1. Handling: Cropamezole™ can produce an abrupt reversal of sedation; therefore, dogs that have recently received Cropamezole™ should be handled with caution. The potential for apprehensive or aggressive behavior should be considered in the handling of dogs emerging from sedation, especially in dogs predisposed to nervousness or fright. Also, avoid situations where a dog might fall.

2. Sedation relapse: While atipamezole does reverse the clinical signs associated with medetomidine or dexmedetomidine sedation, complete physiologic return to pretreatment status may not be immediate or may be temporary, and dogs should be monitored for sedation relapse. Sedation relapse is more likely to occur in dogs that receive an alpha$_2$-agonist by the IV route, compared to dogs that are sedated using the IM route. Animals should be monitored closely for persistent hypothermia, bradycardia, and depressed respiration, until signs of recovery persist.

3. Analgesia reversal: Atipamezole reverses analgesic effects as well as sedative effects. Additional procedures for the control of pain may be required.

4. Debilitated dogs: The safety of atipamezole has not been evaluated in dogs with compromised health. Geriatric, debilitated, and ill dogs are more likely to experience adverse reactions associated with the administration of alpha$_2$-antagonists (as well as alpha$_2$-agonists). Dogs with abnormalities associated with the cardiovascular system are especially at risk.

5. Breeding dogs: Cropamezole™ has not been evaluated in breeding dogs; therefore, the drug is not recommended for use in pregnant or lactating dogs, or in dogs intended for breeding.

6. Minimum age and weight: Cropamezole™ has not been evaluated in dogs less than four months of age or in dogs weighing less than 4.4 lbs (2 kg).

ADVERSE REACTIONS: Occasional vomiting may occur. At times, a period of excitement or apprehensiveness may be seen in dogs treated with atipamezole. Other effects of atipamezole include hypersalivation, diarrhea, and tremors.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet, contact Cronus Pharma LLC at 1-844-227-6687 or 1-844-2-CRONUS. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www. fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY: Atipamezole is a potent alpha$_2$-antagonist which selectively and competitively inhibits alpha$_2$-adrenergic receptors. The result of atipamezole administration in the dog is the rapid recovery from the sedative and analgesic effects produced by the alpha$_2$-adrenergic agonists dexmedetomidine or medetomidine. Atipamezole does not reverse the effects of other classes of sedatives, anesthetics, or analgesics.

Atipamezole is rapidly absorbed following intramuscular injection; maximum serum concentration is reached in approximately 10 minutes. Onset of arousal is usually apparent within 5 to 10 minutes of injection, depending on the depth and duration of dexmedetomidine- or medetomidine-induced sedation. Elimination half-life from serum is less than 3 hours. Atipamezole undergoes extensive hepatic biotransformation, with excretion of metabolites primarily in urine.

Dexmedetomidine or medetomidine activation of peripheral and central alpha$_2$-adrenergic receptors induces a pattern of pharmacological responses that include sedation, reduction of anxiety, analgesia, and bradycardia.

Blood pressure is initially increased due to peripheral vasoconstriction and thereafter drops to normal or slightly below normal levels. A transient, decrease in systolic blood pressure occurs immediately after administration of atipamezole to dexmedetomidine- or medetomidine-sedated dogs, followed by a transient increase in arterial pressure within 10 minutes compared to pre-atipamezole levels. This is the opposite of the response to alpha$_2$-agonist treatment, and is probably due to atipamezole-induced peripheral vasodilation.

Atipamezole administration rapidly abolishes dexmedetomidine- or medetomidine-induced bradycardia, usually within 3 minutes. The magnitude of the effect of atipamezole on heart rate is greater when dexmedetomidine is administered intravenously compared to intramuscularly. Dogs receiving medetomidine or IM dexmedetomidine may not return to pre-sedative heart rates after atipamezole administration and some dogs briefly show heart rate elevations above baseline. Respiratory rate increases following atipamezole injection.

EFFECTIVENESS: One hundred and nine dogs received atipamezole in the field study (55 dogs received the reversal agent following dexmedetomidine; 54 following medetomidine). The mean age was 5.9 years and ranged between 17 weeks and 16 years. The mean weight was 45.5 lbs (20.7 kg), ranging from 4.8 lbs to 117 lbs (2.2 kg to 53.2 kg). Atipamezole was administered by the IM route of administration, within a range of 39-57 minutes after administration of either dexmedetomidine (IV and IM) or medetomidine (IV and IM).

Atipamezole reversed the effects of dexmedetomidine and medetomidine in all cases. In dexmedetomidine treated dogs, the onset of reversal was evident within 5 minutes after administration of atipamezole (57% could stand). Within 15 minutes, 96% of dexmedetomidine treated dogs were standing, 92% responded normally to sound, 86% had a normal muscle tone of jaw, and >90% had a normal pedal reflex response. Responses in dogs treated with medetomidine were similar or slightly later.

Following atipamezole, heart rate increased between 0 and 5 minutes following either alpha$_2$-agonist (IV dexmedetomidine dogs had heart rates from 60 to 85 bpm, and IV medetomidine dogs from 51 to 67 bpm; IM dexmedetomidine dogs had heart rates from 45 to 73 bpm, and IM medetomidine dogs from 52 to 79 bpm). Bradycardia resolved more slowly in the IM treatment groups. The body temperature remained at the same level during the 120 minutes of follow-up after atipamezole administration. Respiratory rates increased toward normal between 0 and 5 minutes after the administration of atipamezole in all treatment groups. Mucous membranes were described as normal after 5 minutes in 91% of dexmedetomidine dogs (IV or IM). By 120 minutes, 96% were normal (after IV dexmedetomidine) or 100% were normal (after IM dexmedetomidine). Many physiological responses were slightly slower to return toward normal when dogs were treated with medetomidine IV or IM.

No adverse events were reported in the atipamezole treated dogs.

ANIMAL SAFETY: Atipamezole was tolerated in healthy dogs receiving 10X the recommended dose and in dogs receiving repeated doses at 1, 3, and 5X the recommended dose, in the absence of an alpha$_2$-agonist. Signs were dose-related and included excitement, panting, trembling, vomiting, soft or liquid feces and scleral injection. At 10X the recommended dose, increases in creatine kinase, AST, and ALT were noted. Creatine kinase also increased in 3 (of 6) dogs in the 3X treatment group. Localized skeletal muscle injury was seen at the injection site but no associated clinical signs or complications were observed. Dogs receiving the recommended atipamezole dose in the absence of medetomidine or dexmedetomidine exhibited no adverse clinical signs. In additional safety studies, adverse events were absent up to the 3X dose of atipamezole when its administration followed medetomidine or dexmedetomidine sedation.

In a separate safety study using a crossover design, 5 dogs received atipamezole after dexmedetomidine (IV and IM). Dexmedetomidine's effects on blood pressure, heart rate, respiratory rate, and cardiac conduction times were reversed by atipamezole. However, heart rate and cardiac conduction times did not return to predexmedetomidine values. Heart rate increases after atipamezole were closer to baseline values in dogs treated with dexmedetomidine IV (compared to IM).

STORAGE INFORMATION: Store at USP controlled room temperature 20° to 25°C (68 to 77°F), with excursions permitted between 15° to 30°C (59 to 86°F). Protect from light.

Use within 28 days of first puncture and maximum allowable punctures are 16 punctures.

HOW SUPPLIED: Cropamezole™ is supplied in 10-mL, multidose vials containing 5.0 mg of atipamezole hydrochloride per mL.

Approved by FDA under ANADA #200-753
Cropamezole™ is the trademark of Cronus Pharma LLC

TAKE TIME. OBSERVE LABEL DIRECTIONS.

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816.
Contact No: 1-844-227-6687
(1-844-2-CRONUS)

Made in India.
October 2021

CLINDAMYCIN HYDROCHLORIDE CAPSULES, USP

For oral use in dogs only

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Clindamycin Hydrochloride Capsules, USP contain clindamycin hydrochloride which is the hydrated salt of clindamycin. Clindamycin is a semisynthetic antibiotic produced by a 7(S)-chlorosubstitution of the 7(R)-hydroxyl group of a naturally produced antibiotic produced by *Streptomyces lincolnensis var. lincolnensis.*

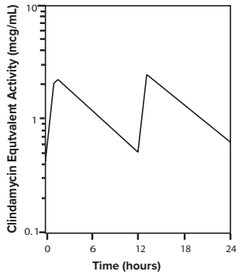
Clindamycin Hydrochloride Capsules, USP (For Use in Dogs Only):
25 mg Capsule, each yellow and colorless capsule contains clindamycin hydrochloride equivalent to 25 mg of clindamycin.
75 mg Capsule, each green and colorless capsule contains clindamycin hydrochloride equivalent to 75 mg of clindamycin.
150 mg Capsule, each blue and colorless capsule contains clindamycin hydrochloride equivalent to 150 mg of clindamycin.
300 mg Capsule, each turquoise and colorless capsule contains clindamycin hydrochloride equivalent to 300 mg of clindamycin.

CLINICAL PHARMACOLOGY

ABSORPTION:
Clindamycin hydrochloride is rapidly absorbed from the canine gastrointestinal tract.

DOG SERUM LEVELS:
Serum levels at or above 0.5 µg/mL can be maintained by oral dosing at a rate of 2.5 mg/lb of clindamycin hydrochloride every 12 hours. This same study revealed that average peak serum concentrations of clindamycin occur 1 hour and 15 minutes after oral dosing. The elimination half -life for clindamycin in dog serum was approximately 5 hours. There was no bioactivity accumulation after a regimen of multiple oral doses in healthy dogs.

Clindamycin Serum Concentrations
2.5 mg/lb (5.5 mg/kg) After B.I.D. Oral
Dose of Clindamycin Hydrochloride Capsules to Dogs



METABOLISM AND EXCRETION: Extensive studies of the metabolism and excretion of clindamycin hydrochloride administered orally in animals and humans have shown that unchanged drug and bioactive and bioinactive metabolites are excreted in urine and feces. Almost all of the bioactivity detected in serum after clindamycin hydrochloride product administration is due to the parent molecule (clindamycin). Urine bioactivity, however, reflects a mixture of clindamycin and active metabolites, especially N-demethyl clindamycin and clindamycin sulfoxide.

SITE AND MODE OF ACTION: Clindamycin is an inhibitor of protein synthesis in the bacterial cell. The site of binding appears to be in the 5OS sub-unit of the ribosome. Binding occurs to the soluble RNA fraction of certain ribosomes, thereby inhibiting the binding of amino acids to those ribosomes. Clindamycin differs from cell wall inhibitors in that it causes irreversible modification of the protein-synthesizing subcellular elements at the ribosomal level.

MICROBIOLOGY: Clindamycin is a lincosaminide antimicrobial agent with activity against a wide variety of aerobic and anaerobic bacterial pathogens. Clindamycin is a bacteriostatic compound that inhibits bacterial protein synthesis by binding to the 5OS ribosomal sub-unit. The minimum inhibitory concentrations (MICs) of Gram-positive and obligate anaerobic pathogens isolated from dogs in the United States are presented in Table 1. Bacteria were isolated in 1998-1999. All MICs were performed in accordance with the Clinical and Laboratory Standards Institute (CLSI).

Table 1. Clindamycin MIC Values (µg/mL) from Diagnostic Laboratory Survey Data Evaluating Canine Pathogens in the U.S. during 1998-99[1]

Organism	Number of Isolates	MIC_{50}	MIC_{85}	MIC_{90}	Range
Soft Tissue/Wound [2]					
Staphylococcus aureus	17	0.5	0.5	≥ 4.0	0.25 - ≥ 4.0
Staphylococcus intermedius	28	0.25	0.5	≥ 4.0	0.125 - ≥ 4.0
Staphylococcus spp.	18	0.5	0.5	≥ 4.0	0.25 - ≥ 4.0
Beta-hemolytic streptococci	46	0.5	0.5	≥ 4.0	0.25 - ≥ 4.0
Streptococcus spp.	11	0.5	≥ 4.0	≥ 4.0	0.25 - ≥ 4.0
Osteomyelitis/Bone[3]					
Staphylococcus aureus	20	0.50	.5	0.5	0.5[4]
Staphylococcus intermedius	15	0.5	≥ 4.0	≥ 4.0	0.25 - ≥ 4.0
Staphylococcus spp.	18	0.5	≥ 4.0	≥ 4.0	0.25 - ≥ 4.0
Beta-hemolytic streptococci	21	0.52	.0	2.0	0.25 - ≥ 4.0
Streptococcus spp.	21	≥ 4.0	≥ 4.0	≥ 4.0	0.25 - ≥ 4.0
Dermal/Skin[5]					
Staphylococcus aureus	25	0.5	≥ 4.0	≥ 4.0	0.25 - ≥ 4.0
Staphylococcus intermedius	48	0.5	≥ 4.0	≥ 4.0	0.125 - ≥ 4.0
Staphylococcus spp.	32	0.5	≥ 4.0	≥ 4.0	0.25 - ≥ 4.0
Beta-hemolytic streptococci	17	0.50	.5	0.5	0.25 – 0.5

1 The correlation between the *in vitro* susceptibility data and clinical response has not been determined.
2 Soft Tissue/Wound: includes samples labeled wound, abscess, aspirate, exudates, draining tract, lesion, and mass.
3 Osteomyelitis/Bone: includes samples labeled bone, fracture, joint, tendon
4 No range, all isolates yielded the same value
5 Dermal/Skin: includes labeled skin, skin swab, biopsy, incision, lip

INDICATIONS: Clindamycin Hydrochloride Capsules, USP (for use in dogs only) are indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below:

Dogs: Skin infections (wounds and abscesses) due to coagulase positive staphylococci (*Staphylococcus aureus* or *Staphylococcus intermedius*).
Deep wounds and abscesses due to *Bacteroides fragilis, Prevotella melaninogenicus, Fusobacterium necrophorum* and *Clostridium perfringens.*

Dental infections due to *Staphylococcus aureus*, *Bacteroides fragilis, Prevotella melaninogenicus, Fusobacterium necrophorum* and *Clostridium perfringens*. **Osteomyelitis** due to *Staphylococcus aureus, Bacteroides fragilis, Prevotella melaninogenicus, Fusobacterium necrophorum* and *Clostridium perfringens*.

CONTRAINDICATIONS: Clindamycin Hydrochloride Capsules, USP are contraindicated in animals with a history of hypersensitivity to preparations containing clindamycin or lincomycin.

Because of potential adverse gastrointestinal effects, do not administer to rabbits, hamsters, guinea pigs, horses, chinchillas or ruminating animals.

WARNINGS: Keep out of reach of children. Not for human use.

PRECAUTIONS: During prolonged therapy of one month or greater, periodic liver and kidney function tests and blood counts should be performed.

The use of Clindamycin Hydrochloride Capsules, USP occasionally results in overgrowth of non-susceptible organisms such as clostridia and yeasts. Therefore, the administration of Clindamycin Hydrochloride Capsules should be avoided in those species sensitive to the gastrointestinal effects of clindamycin **(see CONTRAINDICATIONS)**. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution, and serum clindamycin levels monitored during high-dose therapy.

Clindamycin hydrochloride has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, Clindamycin

Hydrochloride Capsules, USP should be used with caution in animals receiving such agents. Safety in gestating bitches and queens or breeding male dogs has not been established.

ADVERSE REACTIONS: Side effects occasionally observed in either clinical trials or during clinical use were vomiting and diarrhea. To report a suspected adverse reaction call 1-844-227-6687 (1-844-2CRONUS)

DOSAGE AND ADMINISTRATION:
Dogs: Infected Wounds, Abscesses, and Dental Infections
Oral: 2.5-15.0 mg/lb body weight every 12 hours.

Duration: Treatment with Clindamycin Hydrochloride Capsules, USP may be continued up to a maximum of 28 days if clinical judgment indicates. Treatment of acute infections should not be continued for more than three or four days if no response to therapy is seen.

Dosage Schedule:
Capsules
Clindamycin Hydrochloride Capsules, USP 25 mg, administer 1-6 capsules every 12 hours for each 10 pounds of body weight.
Clindamycin Hydrochloride Capsules, USP 75 mg, administer 1-6 capsules every 12 hours for each 30 pounds of body weight.
Clindamycin Hydrochloride Capsules, USP 150 mg, administer 1-6 capsules every 12 hours for each 60 pounds of body weight.
Clindamycin Hydrochloride Capsules, USP 300 mg, administer 1-6 capsules every 12 hours for each 120 pounds of body weight.

Dogs: Osteomyelitis

Oral: 5.0-15.0 mg/lb body weight every 12 hours.

Duration: Treatment with Clindamycin Hydrochloride Capsules is recommended for a minimum of 28 days. Treatment should not be continued for longer than 28 days if no response to therapy is seen.

Dosage Schedule:
Capsules
Clindamycin Hydrochloride Capsules, USP 25 mg, administer 2-6 capsules every 12 hours for each 10 pounds of body weight.
Clindamycin Hydrochloride Capsules, USP 75 mg, administer 2-6 capsules every 12 hours for each 30 pounds of body weight.
Clindamycin Hydrochloride Capsules, USP 150 mg, administer 2-6 capsules every 12 hours for each 60 pounds of body weight.
Clindamycin Hydrochloride Capsules, USP 300 mg, administer 2-6 capsules every 12 hours for each 120 pounds of body weight

ANIMAL SAFETY SUMMARY: Rat and Dog Data: One year oral toxicity studies in rats and dogs at doses of 30, 100 and 300 mg/kg/day (13.6, 45.5 and 136.4 mg/lb/day) have shown clindamycin hydrochloride capsules to be well tolerated. Differences did not occur in the parameters evaluated to assess toxicity when comparing groups of treated animals with contemporary controls. Rats administered clindamycin hydrochloride at 600 mg/kg/day (272.7mg/lb/day) for six months tolerated the drug well; however, dogs orally dosed at 600 mg/kg/day (272.7 mg/lb/day) vomited, had anorexia, and subsequently lost weight. At necropsy these dogs had erosive gastritis and focal areas of necrosis of the mucosa of the gallbladder.

Safety in gestating bitches or breeding males has not been established.

STORAGE: Store at controlled room temperature 68° to 77°F (20° to 25°C).

HOW SUPPLIED: Clindamycin Hydrochloride Capsules are available as:
25 mg – bottles of 200
75 mg – bottles of 200
150 mg – bottles of 100 and 500
300 mg – bottles of 100

To report suspected adverse drug events, for technical assistance or to obtain a copy of the safety data sheet (SDS), contact Cronus Pharma LLC at 1-844-227-6687 or 1-844-2-CRONUS. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at https://www.fda.gov/animal-veterinary/safety-health.

Approved by FDA under ANADA #200-298

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816.
Contact No: 1-844-227-6687
(1-844-2-CRONUS)

Made in India
Distributed by:
Cronus Pharma, LLC
2 Tower Center Boulevard, Suite 1101A,
East Brunswick, NJ 08816
Contact No: 1-844-227-6687 (1-844-2-CRONUS)
e-Fax No: 732-647-1272
Email: contact@cronuspharma.com
PIC01320-03

TAKE TIME.
OBSERVE LABEL
DIRECTIONS.

Issued: 06/2019

CLINDAMYCIN HYDROCHLORIDE ORAL SOLUTION

Approved by FDA under ANADA #200-193
Approved for use in dogs and cats

RECOMMENDED DOG DOSAGE: For therapy of wounds, abscesses and dental infections, orally administer 2.5-15.0 mg/lb (1-6 mL/10 lb) body weight every 12 hours. For therapy of osteomyelitis orally administer 5.0-15.0 mg/lb (2-6 mL/10 lb) body weight every 12 hours.

RECOMMENDED CAT DOSAGE: For therapy of wounds, abscesses and dental infections, orally administer 1-3 mL/5 lb body weight once every 24 hours depending on the severity of the condition.

WARNING: Keep out of reach of children. Not for human use.

Store at controlled room temperature 20°-25°C (68°-77°F).

Each mL contains: Clindamycin hydrochloride equivalent to clindamycin 25 mg and ethyl alcohol, 8.64%.

See label insert for complete product Information.

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Clindamycin Hydrochloride Oral Solution contains clindamycin hydrochloride which is the hydrated salt of clindamycin. Clindamycin is a semisynthetic antibiotic produced by a 7(S)-chlorosubstitution of the 7(R)-hydroxyl group of naturally produced antibiotic produced by *Streptomyces lincolnensis var. lincolnensis*.

Clindamycin Hydrochloride Oral Solution (for use in dogs and cats) is a palatable formulation intended for oral administration. Each mL of Clindamycin Hydrochloride Oral Solution contains clindamycin hydrochloride equivalent to 25 mg clindamycin; and ethyl alcohol, 8.64%.

ACTIONS: Site and Mode of Action: Clindamycin is an inhibitor of in protein synthesis in the bacterial cell. The site of binding appears to be in the 50S sub-unit of the ribosome. Binding occurs to the soluble RNA fraction of certain ribosomes, thereby inhibiting the binding of amino acids to those ribosomes. Clindamycin differs from cell wall inhibitors in that it causes irreversible modification of the protein-synthesizing subcellular elements at the ribosomal level.

MICROBIOLOGY: Clindamycin is a lincosaminide antimicrobial agent with activity against a wide variety of aerobic and anaerobic bacterial pathogens. Clindamycin is a bacteriostatic compound that inhibits bacterial protein synthesis by binding to the 50S ribosomal sub-unit. The minimum inhibitory concentrations (MICs) of Gram-positive and obligate anaerobic pathogens isolated from dogs and cats in the United States are presented in Table 1 and Table 2. Bacteria were isolated in 1998-1999. All MICs were performed in accordance with the National Committee for Clinical Laboratory Standards (NCCLS).

Table 1. Clindaymcin MIC Values (µg/mL) from Diagnostic Laboratory Survey Data Evaluating Canine Pathogens in the U.S. during 1998-99[1]

Organism	Number of Isolates	MIC_{50}	MIC_{85}	MIC_{90}	Range
Soft Tissue/Wound[2]					
Staphylococcus aureus	17	0.5	0.5	≥4.0	0.25->4.0
Staphylococcus intermedius	28	0.25	0.5	≥4.0	0.125->4.0
Staphylococcus spp.	18	0.5	0.5	≥4.0	0.25->4.0
Beta-hemolytic streptococci	46	0.5	0.5	≥4.0	0.25->4.0
Streptococcus spp.	11	0.5	≥4.0	≥4.0	0.25->4.0
Osteomyelitis/Bone[3]					
Staphylococcus aureus	20	0.5	0.5	0.5	0.5[4]
Staphylococcus intermedius	15	0.5	≥4.0	≥4.0	0.25->4.0
Staphylococcus spp.	18	0.5	≥4.0	≥4.0	0.25->4.0
Beta-hemolytic streptococci	21	0.5	2.0	2.0	0.25->4.0
Streptococcus spp.	21	≥4.0	≥4.0	≥4.0	0.25->4.0
Dermal/Skin[5]					
Staphylococcus aureus	25	0.5	≥4.0	≥4.0	0.25->4.0
Staphylococcus intermedius	48	0.5	≥4.0	≥4.0	0.125->4.0
Staphylococcus spp.	32	0.5	≥4.0	≥4.0	0.25->4.0
Beta-hemolytic streptococci	17	0.5	0.5	0.5	0.25-0.5

1. The correlation between the *in vitro* susceptibility data and clinical response has not been determined.
2. Soft Tissue/Wound: includes samples labeled wound, abscess, aspirate, exudates, draining tract, lesion, and mass
3. Osteomyelitis/Bone: includes samples labeled bone, fracture, joint, tendon
4. No range, all isolates yielded the same value
5. Dermal/Skin: includes samples labeled skin, skin swab, biopsy, incision, lip

Table 2. Clindamycin MIC Values (µg/mL) from Diagnostic Laboratory Survey Data Evaluating Feline Pathogens from Wound and Abscess Samples in the U.S. during 1998[1]

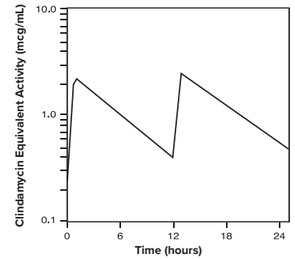
Organism	Number of Isolates	MIC_{50}	MIC_{90}	Range
Bacteroides/ Prevotella	30	0.06	4.0	≤0.015-4.0
Fusobacterium spp.	17	0.25	0.25	≤0.015-0.5
Peptostreptococcus spp.	18	0.13	0.5	≤0.015-8.0
Porphyromonas spp.	13	0.06	0.25	≤0.015-8.0

1. The correlation between the *in vitro* susceptibility data and clinical response has not been determined.

PHARMACOLOGY: Absorption: Clindamycin hydrochloride is rapidly absorbed from the canine and feline gastrointestinal tract.

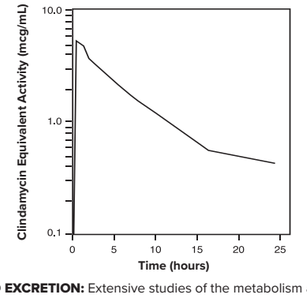
Dog Serum Levels: Serum levels at or above 0.5 µg/mL can be maintained by oral dosing at a rate of 2.5mg/lb of clindamycin hydrochloride every 12 hours. This same study revealed that average peak serum concentrations of clindamycin occur 1 hour and 15 minutes after oral dosing. The elimination half-life for clindamycin in dog serum was approximately 5 hours. There was no bioactivity accumulation after a regimen of multiple oral doses in healthy dogs.

Clindamycin Serum Concentrations
2.5 mg/lb (5.5 mg/kg) After B.I.D.
Oral Dose of Clindamycin Hydrochloride
Capsules to Dogs



Cat Serum Levels: Serum levels at or above 0.5µg/mL can be maintained by oral dosing at a rate of 5mg/lb of clindamycin hydrochloride solution every 24 hours. The average peak serum concentration of clindamycin occurs approximately 1 hour after oral dosing. The elimination half-life of clindamycin in feline serum is approximately 7.5 hours. In healthy cats, minimal accumulation occurs after multiple oral doses of clindamycin hydrochloride, and steady-state should be achieved by the third dose.

Clindamycin Serum Concentrations
5mg/lb (11 mg/kg) After Single Oral
Dose of Clindamycin Hydrochloride
Oral Solution to Cats



METABOLISM AND EXCRETION: Extensive studies of the metabolism and excretion of clindamycin hydrochloride administered orally in animals and humans have shown that unchanged drug and bioactive and bioinactive metabolites are excreted in urine and feces. Almost all of the bioactivity deteted in serum after clindamycin hydrochloride product administration is due to the parent molecule (clindamycin). Urine bioactivity, however, reflects a mixture of clindamycin and active metabolites, especially N-demethyl

clindamycin and clindamycin sulfoxide.

ANIMAL SAFETY SUMMARY: Rat and Dog Data: One year oral toxicity studies in rats and dogs at doses of 30, 100 and 300 mg/kg/day (13.6, 45.5 and 136.4 mg/lb/day) have shown clindamycin hydrochloride to be well tolerated. Differences did not occur in the parameters evaluated to assess toxicity when comparing groups of treated animals with contemporary controls. Rats administered clindamycin hydrochloride at 600 mg/kg/day (272.7 mg/lb/day) for six months tolerated the drug well; however, dogs orally dosed at 600 mg/kg/day (272.7mg/lb/day) vomited, had anorexia, and subsequently lost weight. At necropsy these dogs had erosive gastritis and focal areas of necrosis of the mucosa of the gall bladder. Safety in gestating bitches or breeding males has not been established.

Cat Data: The recommended daily therapeutic dose range for Clindamycin Hydrochloride Oral Solution is 11 to 33 mg/kg/day (5 to 15 mg/lb/day) depending on the severity of the condition. Clindamycin Hydrochloride Solution was tolerated with little evidence of toxicity in domestic shorthair cats when administered orally at 10x the minimum recommended therapeutic daily dose (11mg/kg; 5 mg/lb) for 15 days, and at doses up to 5x the minimum recommended therapeutic dose for 42 days. Gastrointestinal tract upset (soft feces to diarrhea) occurred in control and treated cats with emesis occurring at doses 3x or greater than the minimum recommended therapeutic dose (11 mg/kg/day; 5 mg/b/day). Lymphocytic inflammation of the gallbladder was noted in a greater number of treated cats at the 110 mg/kg/day (50 mg/lb/day) dose level than for control cats. No other effects were noted. Safety in gestating queens or breeding male cats has not been established.

INDICATIONS: Clindamycin Hydrochloride Oral Solution (for use in dogs and cats) is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below:

Dogs: Skin infections (wounds and abscesses) due to coagulase positive staphylococci *(Staphylococcus aureus or Staphylococcus intermedius).* **Deep wounds and abscesses** due to *Bacteroides fragilis, Prevotella melaninogenicus, Fusobacterium necrophorum Clostridium perfringens.* **Dental infections** *Staphylococcus aureus, Bacteroides fragilis, Prevotella melaninogenicus, Fusobacterium necrophorum Clostridium perfringens.* **Osteomyelitis** due to *Staphylococcus aureus, Bacteroides fragilis, Prevotella melaninogenicus, Fusobacterium necrophorum Clostridium perfringens.*

Cats: Skin infections (wounds and abscesses) to *Staphylococcus aureus, Staphylococcus intermedius, Streptococcus* spp. **Deep wounds and absces** to *Clostridium perfringens* and *Bacteroides fragilis*. **Dental infections** due to *Staphylococcus aureus, Staphylococcus intermedius, Streptococcus Clostridium perfringens* and *Bacteroides fragilis*.

CONTRAINDICATIONS: Clindamycin Hydrochloride Oral Solution is contraindicated in animals with history of hypersensitivity to preparations containing clindamycin or lincomycin. Because of potential adverse gastrointestinal effects, do not administer to rabbits, hamsters, guinea pigs, horses, chinchillas or ruminating animals.

WARNINGS: Keep out of reach of children. Not for human use.

PRECAUTIONS: During prolonged therapy of one month or greater, periodic liver and kidney function tests and blood counts should be performed.

The use of clindamycin hydrochloride occasionally results in overgrowth of non-susceptible organisms such as clostridia and yeasts. Therefore, the administration of clindamycin hydrochloride should be avoided in those species sensitive to the gastrointestinal effects of clindamycin **(see CONTRAINDICATIONS)**. Should superinfection occur, appropriate measures should be taken as indicated by the clinical situation.

Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution, and serum clindamycin levels monitored during high dose therapy.

Clindamycin hydrochloride has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, clindamycin hydrochloride should be used with caution in animals receiving such agents. Safety in gestating bitches and queens or breeding male dogs and cats has not been established.

ADVERSE REACTIONS: Side effects occasionally observed in either clinical trials or during clinical use were vomiting and diarrhea.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Cronus Pharma LLC at 1-844-227-6687 (1-844-2-CRONUS).

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

DOSAGE AND ADMINISTRATION: Dogs: Infected Wounds, Abscesses and Dental Infections
Oral: 2.5-15.0 mg/lb body weight every 12 hours.
Duration: Treatment with clindamycin hydrochloride products may be continued up to a maximum of 28 days if clinical judgment indicates. Treatment of acute infections should not be continued for more than three or four days if no response to therapy is seen.
Dosage Schedule:
Clindamycin Hydrochloride Oral Solution
Administer 1-6 mL/10 lb body weight every 12 hours.
Dogs: Osteomyelitis
Oral: 5.0-15.0 mg/lb body weight every 12 hours.
Duration: Treatment with Clindamycin Hydrochloride Oral Solution is recommended a for a minimum of 28 days. Treatment should not be continued for longer than 28 days if no response to therapy is seen.

Dosage Schedule:
Clindamycin Hydrochloride Oral Solution
Administer 2-6 mL/10 lb body weight every 12 hours.
Cats: Infected Wounds, Abscesses and Dental Infections
Oral: 5.0 to 15.0 mg/lb body weight once every 24 hours depending on the severity of the condition.
Duration: Treatment with Clindamycin Hydrochloride Oral Solution may be continued up to a maximum of 14 days if clinical judgment indicates. Treatment of acute infections should not be continued for more than three to four days if no clinical response to therapy is seen.
Dosage Schedule:
Clindamycin Hydrochloride Oral Solution, to provide 5.0 mg/lb, administer 1mL/5 lb body weight once every 24 hours; to provide 15.0 mg/lb, administer 3 mL/5 lb body weight once every 24 hours.

HOW SUPPLIED: Clindamycin Hydrochloride Oral Solution is available as 20 mL filled in 30 mL bottles (25 mg/mL) supplied in packers containing 12 cartoned bottles with direction labels and calibrated dosing droppers.
NDC 69043-012-02

Store at controlled room temperature 20°-25°C (68°-77°F).

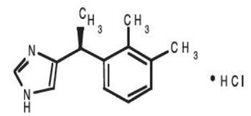
Manufactured for:
Cronus Pharma LLC
East Brunswick, NJ 08816
ELC01202-00
Issued: 09-2022

DEXMEDVET™ (DEXMEDETOMIDINE HYDROCHLORIDE)

Sterile Injectable Solution – 0.5 mg/mL
Intramuscular and Intravenous use in Dogs
Intramuscular use in Cats
Sedative, Analgesic, Preanesthetic

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: DexmedVet™ (dexmedetomidine hydrochloride) is a synthetic alpha$_2$-adrenoreceptor agonist with sedative and analgesic properties. The chemical name is (+)-4-[1-(2,3-dimethylphenyl) ethyl]-1H-imidazole monohydrochloride. It is a white, or almost white, crystalline, water soluble substance having a molecular weight of 236.7. The molecular formula is $C_{13}H_{16}N_2 \cdot HCl$ and the structural formula is:



Each mL of DexmedVet™ contains 0.5 mg dexmedetomidine hydrochloride, 1.6 mg methylparaben (NF), 0.2 mg propylparaben (NF), 9.0 mg sodium chloride (USP), and water for injection (USP), q.s.

INDICATIONS: DexmedVet™ is indicated for use as a sedative and analgesic in dogs and cats to facilitate clinical examinations, clinical procedures, minor surgical procedures, and minor dental procedures. DexmedVet™ is also indicated for use as a preanesthetic to general anesthesia in dogs and cats.

DOSAGE AND ADMINISTRATION: Dogs: Sedation and Analgesia: 500 mcg/m² intramuscularly (IM) or 375 mcg/m² intravenously (IV). Preanesthesia: 125 or 375 mcg/m² IM. The choice of preanesthetic dose depends on the duration and severity of the procedure, as well as the anesthetic regime. The following two tables may be used to determine the correct dexmedetomidine dosage. **Note that the mcg/kg dosage decreases as body weight increases.** For example, dogs weighing 2 kg are dosed at 28.1 mcg/kg dexmedetomidine IV, compared to dogs weighing 80 kg that are dosed at 8.7 mcg/kg. Due to the small volume of administration, accurate dosing is not possible in dogs weighing less than 2 kg (4.4 lb).

Table 1: CANINE SEDATION/ANALGESIA DOSE TABLE: Intravenous (IV) and intramuscular (IM) dosing on the basis of body weight.

DexmedVet™ 0.5 mg/mL					
Sedation/analgesia in dogs					
Dog Weight		Dexmedetomidine 375 mcg/m² IV		Dexmedetomidine 500 mcg/m² IM	
lbs	Kg	mcg/kg	mL	mcg/kg	mL
4.4-7	2-3	28.1	**0.12**	40	**0.15**
7.1-9	3.1-4	25	**0.15**	35	**0.2**
9.1-11	4.1-5	23	**0.2**	30	**0.3**
11.1-22	5.1-10	19.6	**0.29**	25	**0.4**
22.1-29	10.1-13	16.8	**0.38**	23	**0.5**
29.1-33	13.1-15	15.7	**0.44**	21	**0.6**
33.1-44	15.1-20	14.6	**0.51**	20	**0.7**
44.1-55	20.1-25	13.4	**0.6**	18	**0.8**
55.1-66	25.1-30	12.6	**0.69**	17	**0.9**
66.1-73	30.1-33	12	**0.75**	16	1
73.1-81	33.1-37	11.6	**0.81**	15	**1.1**
81.1-99	37.1-45	11	**0.9**	14.5	**1.2**
99.1-110	45.1-50	10.5	**0.99**	14	**1.3**
110.1-121	50.1-55	10.1	**1.06**	13.5	**1.4**
121.1-132	55.1-60	9.8	**1.13**	13	**1.5**
132.1-143	60.1-65	9.5	**1.19**	12.8	**1.6**
143.1-154	65.1-70	9.3	**1.26**	12.5	**1.7**
154.1-176	70.1-80	9	**1.35**	12.3	**1.8**
>176	>80	8.7	**1.42**	12	**1.9**

Table 2: CANINE PREANESTHESIA DOSE TABLE: Intramuscular (IM) dosing on the basis of body weight.

DexmedVet™ 0.5 mg/mL					
Preanesthesia in dogs					
Dog Weight		Dexmedetomidine 125 mcg/m² IM		Dexmedetomidine 375 mcg/m² IM	
lbs	Kg	mcg/kg	mL	mcg/kg	mL
4.4-7	2-3	9.4	**0.04**	28.1	**0.12**
7.1-9	3.1-4	8.3	**0.05**	25	**0.15**
9.1-11	4.1-5	7.7	**0.07**	23	**0.2**
11.1-22	5.1-10	6.5	**0.1**	19.6	**0.29**
22.1-29	10.1-13	5.6	**0.13**	16.8	**0.38**
29.1-33	13.1-15	5.2	**0.15**	15.7	**0.44**
33.1-44	15.1-20	4.9	**0.17**	14.6	**0.51**
44.1-55	20.1-25	4.5	**0.2**	13.4	**0.6**
55.1-66	25.1-30	4.2	**0.23**	12.6	**0.69**
66.1-73	30.1-33	4	**0.25**	12	**0.75**
73.1-81	33.1-37	3.9	**0.27**	11.6	**0.81**
81.1-99	37.1-45	3.7	**0.3**	11	**0.9**
99.1-110	45.1-50	3.5	**0.33**	10.5	**0.99**
110.1-121	50.1-55	3.4	**0.35**	10.1	**1.06**
121.1-132	55.1-60	3.3	**0.38**	9.8	**1.13**
132.1-143	60.1-65	3.2	**0.4**	9.5	**1.19**
143.1-154	65.1-70	3.1	**0.42**	9.3	**1.26**
154.1-176	70.1-80	3	**0.45**	9	**1.35**
>176	>80	2.9	**0.47**	8.7	**1.42**

The use of dexmedetomidine as a preanesthetic markedly reduces anesthetic requirements in dogs. Injectable induction drug requirements for intubation will be reduced between 30% and 60%, depending on the choice of anesthetic and the dexmedetomidine preanesthetic dose. The concentration of inhalation maintenance anesthetic will be reduced between 40% and 60%, depending on the dose of dexmedetomidine. The anesthetic dose should always be titrated against the response of the patient. The choice of anesthetic is left to the discretion of the veterinarian.

Cats: Sedation, Analgesia and Preanesthesia: 40 mcg/kg intramuscularly (IM). This dose can also be used as a preanesthetic and has been shown to **markedly reduce anesthetic requirements in cats.** Injectable anesthetic drug requirements for intubation were reduced up to 49%, depending on the choice of induction drug. The concentration of inhalation maintenance anesthetic was reduced between 35% and 44%, depending on the choice of induction drug. The anesthetic dose should always be titrated against the response of the patient.

The following table may be used to determine the correct dexmedetomidine dosage for cats based on body weight.

Table 3: FELINE DOSE TABLE: Intramuscular (IM) dosing on the basis of body weight in cats.

DexmedVet™ 0.5 mg/mL			
Sedation/analgesia and preanesthesia in cats			
Cat Weight		Dexmedetomidine 40 mcg/kg IM	
lbs	kg	mcg/kg	mL
2-4	1-2	40	**0.1**
4.1-7	2.1-3	40	**0.2**
7.1-9	3.1-4	40	**0.3**
9.1-13	4.1-6	40	**0.4**
13.1-15	6.1-7	40	**0.5**
15.1-18	7.1-8	40	**0.6**
18.1-22	8.1-10	40	**0.7**

It is recommended that dogs and cats be fasted for 12 hours before treatment with DexmedVet™. An eye lubricant should be applied to cats to prevent corneal desiccation that may result from a reduction in the blink reflex. Following injection of DexmedVet™, the animal should be allowed to rest quietly for 15 minutes; sedation and analgesia occur within 5 to 15 minutes, with peak effects at 30 minutes after dexmedetomidine.

CONTRAINDICATIONS: Do not use DexmedVet™ in dogs or cats with cardiovascular disease, respiratory disorders, liver or kidney diseases, or in conditions of shock, severe debilitation, or stress due to extreme heat, cold or fatigue. As with all alpha$_2$-adrenoceptor agonists, the potential for isolated cases of hypersensitivity, including paradoxical response (excitation), exists.

WARNINGS: Human safety: Not for human use. Keep out of reach of children. Dexmedetomidine hydrochloride can be absorbed following direct exposure to skin, eyes, or mouth, and may cause irritation. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing.

Appropriate precautions should be taken while handling and using filled syringes. Accidental topical (including ocular) exposure, oral exposure, or exposure by injection could cause adverse reactions, including sedation, hypotension, and bradycardia. Seek medical attention immediately.

Users with cardiovascular disease (for example, hypertension or ischemic heart disease) should take special precautions to avoid any exposure to this product.

Caution should be exercised when handling sedated animals. Handling or any other sudden

stimuli, including noise, may cause a defense reaction in an animal that appears to be heavily sedated.

The safety data sheet (SDS) contains more detailed occupational safety information. To report adverse reactions in users or to obtain a copy of the SDS for this product call 1-844-227-6687.

Note to physician: This product contains an alpha$_2$-adrenergic agonist.

Animal safety: Dexmedetomidine should not be administered in the presence of preexisting hypotension, hypoxia, or bradycardia. Due to the pronounced cardiovascular effects of dexmedetomidine, only clinically healthy dogs and cats (ASA classes I and II) should be treated. Animals should be frequently monitored for cardiovascular function and body temperature during sedation or anesthesia. Dexmedetomidine sedation is not recommended for cats with respiratory disease.

The use of dexmedetomidine as a preanesthetic in dogs and cats significantly reduces the amount of induction and maintenance anesthetic requirements. Careful patient monitoring during anesthetic induction and maintenance is necessary to avoid anesthetic overdose.

PRECAUTIONS: Apnea may occur with dexmedetomidine use. In the event of apnea, additional oxygen should be supplied. Administration of atipamezole to dogs is warranted when apnea is accompanied by bradycardia and cyanotic mucous membranes.

Adverse reaction reports for dexmedetomidine in cats include rare events of severe dyspnea and respiratory crackles diagnosed as acute pulmonary edema. Dyspnea due to the delayed onset of pulmonary edema could develop in rare instances up to three days after dexmedetomidine administration. Some of these acute and delayed pulmonary edema cases have resulted in death although this was not observed in the feline clinical field studies with dexmedetomidine.

In dogs, intramuscular atipamezole may be routinely used to rapidly reverse the effects of dexmedetomidine. Since analgesic as well as sedative effects will be reversed, pain management may need to be addressed.

In cats, atipamezole has not been evaluated as a routine dexmedetomidine reversal agent. In cats, cases of dyspnea following atipamezole administration have been reported.

Dexmedetomidine has not been evaluated in the presence of other preanesthetics in cats. Although not observed in the feline field studies, death has been reported in cats receiving dexmedetomidine in conjunction with ketamine and butorphanol.

Analgesia resulting from preanesthetic dexmedetomidine may not provide adequate pain control during the postoperative or postprocedural period. Additional pain management should be addressed as needed.

Following administration of dexmedetomidine, a decrease in body temperature is likely to occur unless externally maintained. Once established, hypothermia may persist longer than sedation and analgesia. To prevent hypothermia, treated animals should be kept warm and at a constant temperature during the procedure, and until full recovery.

Nervous or excited animals with high levels of endogenous catecholamines may exhibit a reduced pharmacological response to alpha$_2$-adrenoceptor agonists like dexmedetomidine (ineffectiveness). In agitated animals, the onset of sedative/analgesic effects could be slowed, or the depth and duration of effects could be diminished or nonexistent. Therefore, allow dogs and cats to rest quietly for 10 to 15 minutes after injection. Repeat dosing has not been evaluated.

Administration of anticholinergic agents in dogs or cats at the same time or after dexmedetomidine could lead to adverse cardiovascular effects (secondary tachycardia, prolonged hypertension, and cardiac arrhythmias[1, 2, 3]). However, an anticholinergic drug may be administered to dogs at least 10 minutes *before* dexmedetomidine for the prevention of the dexmedetomidine-induced reduction in heart rate. Therefore, the routine use of anticholinergics simultaneously with, or after dexmedetomidine in dogs or cats, is not recommended **(see ANIMAL SAFETY).**

Spontaneous muscle contractions (twitching) can be expected in some dogs sedated with dexmedetomidine.

Dexmedetomidine has been evaluated only in fasted dogs; therefore, its effects on fed dogs (for example, the occurrence of vomiting) have not been characterized. In cats, there is a high frequency of vomition whether fed or fasted; therefore, fasting is recommended to reduce stomach contents.

Dexmedetomidine has not been evaluated in dogs younger than 16 weeks of age, in cats younger than 12 weeks of age, or in geriatric dogs
and cats.

Dexmedetomidine has not been evaluated for use in breeding, pregnant, or lactating dogs or cats.

ADVERSE REACTIONS: Canine sedation/analgesia field study: In the field study safety analysis, 106 dogs received dexmedetomidine and 107 received medetomidine. Dogs ranged from 16 weeks to 16 years of age, representing 49 breeds. The following table shows the number of dogs displaying each clinical observation (some dogs experienced more than one adverse reaction).

Table 4: Adverse reactions during the canine sedation/analgesia field study

	Dexmedetomidine Total n= 106	Medetomidine Total n=107
Ausculted unidentified arrhythmias	19	20
Severe bradycardia requiring treatment	1	1
Apnea requiring treatment	1	0
Slow onset of sedation (exceeding 30 minutes)	1	1
Ineffectiveness (dog standing throughout the study)	3	2
Severe hypothermia requiring treatment	2	0
Prolonged recovery	1	4

The occurrence of ausculted unidentified arrhythmias (some at multiple time points) decreased following the administration of atipamezole.

Canine preanesthesia field study: The preanesthesia field study safety analysis included 192 dogs, between 5 months and 15 years of age, representing 43 breeds enrolled for elective procedures conducted under general anesthesia. The following table shows the number of dogs within a treatment group that showed each clinical sign (dogs may have experienced more than one adverse reaction).

Table 5: Adverse reactions during the canine preanesthesia field study

	Treatment Groups					
Induction Anesthetic:	Propofol			Barbiturate		
Preanesthetic Dose:	0 mcg/m^2 n=32	125 mcg/m^2 n=32	375 mcg/m^2 n=32	0 mcg/m^2 n=32	125 mcg/m^2 n=32	375 mcg/m^2 n=32
Emesis	4	7	4	2	3	6
Ventricular premature contractions	0	2	0	4	1	0
Diarrhea	1	0	0	3	1	1
Self trauma	0	2	1	2	1	0
Severe bradycardia	0	0	1	0	0	1
Tachycardia	0	0	0	1	1	0
Urinary incontinence	0	0	0	0	0	1

Other clinical signs observed in dogs treated with dexmedetomidine include decreased respiratory rate and hypothermia.

Feline sedation/analgesia field study: The field study safety analysis included 242 cats (122 received dexmedetomidine; 120 received xylazine), 6 months to 17 years of age, and representing 19 breeds. The following table shows the number of cats reported with an adverse reaction (cats may have experienced more than one adverse reaction).

Table 6: Adverse reactions during the feline field study

	Dexmedetomidine n = 122	Xylazine n = 120
Vomiting	70	82
Urinary incontinence	6	11
Hypersalivation	4	5
Involuntary defecation	4	1
Hypothermia	2	1
Diarrhea	2	0
Arrhythmia	1	2
Corneal ulcer	1	0
Cyanosis	1	0
Dyspnea	1	0

The most frequently observed adverse reaction was vomiting in both fasted and fed cats. Other infrequent clinical signs observed in cats treated with dexmedetomidine included fatigue, anorexia, cystitis, and peripheral vascular disorder.

One incidence of dyspnea was reported, 43 minutes after dexmedetomidine administration during an oral examination/dental procedure. Prior to dexmedetomidine, the cat was free of clinical signs, but had a history of asthma and respiratory infection. The cat responded successfully to treatment.

Feline preanesthesia field study: The field study safety analysis included 184 cats (116 received dexmedetomidine; 68 received saline), 12 weeks to 16 years of age, and representing 11 breeds. The following table shows the number of cats reported with an adverse reaction (cats may have experienced more than one adverse reaction).

Table 7. Adverse reactions during the feline preanesthesia field study

Induction Anesthetic	Ketamine		Propofol	
Preanesthetic	**Saline n=37**	**Dexmedetomidine n=64**	**Saline n=31**	**Dexmedetomidine n=52**
Emesis	2	20	1	12
Pale mucous membranes		11		9
Decreased body temperature		4		
Retching		1	1	3
Heart murmur				2
Loose stool		2		
Corneal injury	1			
Apnea		1		
Behavioral change			1	
Fluid in endotracheal tube			1	

One case of apnea was reported in a cat that received ketamine as the induction agent. This cat required artificial ventilation from the start of the procedure until 30 minutes into recovery when the cat began to breathe on its own. The cat recovered without further problems.

POST APPROVAL EXPERIENCE: The following adverse events were obtained from post-approval adverse drug events reported for dexmedetomidine hydrochloride sterile injectable solution from 2007-2009. Not all adverse reactions are reported. Some adverse reactions occurred when dexmedetomidine hydrochloride was used alone for sedation; most occurred when dexmedetomidine hydrochloride was used in the presence of anesthetics and/or other preanesthetics. It is not always possible to reliably estimate the frequency of an adverse event or to establish a causal relationship to the drug, especially when multiple drugs are administered. The following reported adverse events are listed in decreasing order of frequency:

Dogs: ineffective for sedation, death, bradycardia, cardiac arrest, apnea, convulsions, vomiting, prolonged sedation, elevated temperature, and delayed sedation.

Cats: ineffective for sedation, death, cardiac arrest, vomiting, apnea, prolonged sedation, hypersalivation, hypothermia, bradycardia, cyanotic mucous membranes, sedation too brief, and dyspnea.

CONTACT INFORMATION: To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Cronus Pharma LLC at 1-844-227-6687. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

INFORMATION FOR OWNERS: Owners should notify their veterinarian immediately if their cat experiences difficulty breathing due to the rare possibility of delayed onset of pulmonary edema which has been associated with administration of alpha$_2$-adrenergic agonists in cats.

CLINICAL PHARMACOLOGY: Dexmedetomidine is a potent non-narcotic alpha$_2$-adrenoceptor agonist which produces sedation and analgesia. These effects are dose dependent in depth and duration. Blood pressure is initially increased due to peripheral vasoconstriction, subsequently dropping to normal or slightly below normal levels. Vasoconstriction may cause mucous membranes to appear pale or mildly cyanotic. This initial vasopressor response is accompanied by a compensatory marked decrease in heart rate mediated by a vagal baroreceptor. The peripheral pulse may feel weak and a transient change in the conductivity of the cardiac muscle may occur, as evidenced by first and second degree atrioventricular blocks. Other arrhythmias may occur. Dexmedetomidine also decreases the respiratory rate and decreases body temperature. The magnitude and duration of the decrease in body temperature is dose dependent. Dexmedetomidine causes depression of gastrointestinal motility due to decrease in smooth muscle activity, increases in blood glucose levels due to inhibition of insulin release, and increases in production of urine. Spontaneous muscle contractions (twitching) can be expected in some dogs sedated with dexmedetomidine. Vomiting in cats has been associated with alpha$_2$-adrenergic agonist central stimulation of the brain[4].

EFFECTIVENESS: Canine sedation/analgesia field study: Dexmedetomidine was evaluated in a masked, controlled, multi-site field study, using parallel treatment groups. Effectiveness was evaluated in 200 (of 213) healthy client-owned dogs, ranging in age between 16 weeks and 16 years of age, and in size between 4.8 lbs and 141 lbs (2.2 kg and 64 kg). Dogs admitted to veterinary clinics for various procedures requiring sedation and/or analgesia received either dexmedetomidine or medetomidine once, by IV or IM injection. Procedures included dental care, radiography, minor skin tumor removal, and treatment of otitis.

Sedation and analgesia occurred within 5 minutes after IV dexmedetomidine, and within 15 minutes after IM dexmedetomidine, with peak effects approximately at 15 or 30 minutes, respectively. Effects waned by approximately two hours after IV administration, and by three hours using the IM route. Dexmedetomidine and medetomidine showed comparable clinical effects.

Cardiac rhythms were evaluated by auscultation. Bradycardia occurred within 5 to 15 minutes after IV dexmedetomidine or medetomidine, and within 15 to 30 minutes after either drug given IM. Sixty-four dexmedetomidine-treated dogs and 50 medetomidine-treated dogs were observed with bradycardia.

Adverse reactions during the field study included ausculted unidentified arrhythmias, apnea, hypothermia, and ineffectiveness **(see ADVERSE REACTIONS).**

Eleven dogs received concomitant medication during the field study, including amoxicillin, cephalexin, triamcinolone, methyl-prednisolone acetate, neomycin, nystatin, thiostrepton, acepromazine, atropine, and atipamezole.

The results of this field study demonstrate that dexmedetomidine produces satisfactory levels of sedation and analgesia for clinical examinations and procedures, minor surgical procedures, and minor dental procedures.

Canine preanesthesia field study: The use of dexmedetomidine as a preanesthetic was evaluated in a controlled, multi-site field study, using parallel treatment groups. Effectiveness was evaluated in 192 healthy, client-owned dogs, between 5 months and 15 years of age, weighing 4 to 196 lbs (2 kg to 89 kg). Dogs received IM dexmedetomidine or saline as a preanesthetic to general anesthesia. All dogs were induced by an injectable anesthetic; half of the dogs were maintained with an inhalation anesthetic. Procedures included orchiectomy, ovariohysterectomy, skin surgery, radiography, physical examination, dental procedures, ear cleaning, anal sac treatment, and grooming.

Compared to saline controls, dexmedetomidine IM reduced induction drug requirements by 30-36% (at 125 mcg/m^2) and by 38-61% (at 375 mcg/m^2). Inhalation anesthetic requirements were 40-60% less for dexmedetomidine-preanesthetized dogs. The number of dogs with clinical signs of pain was less for at least 30 minutes after the procedure in dogs treated with 375 mcg/m2 dexmedetomidine, compared to saline controls.

Recovery times were dose dependent, averaging 15-32 minutes to extubation and 71-131 minutes to standing recovery (longer times correspond to higher dexmedetomidine dose). Recovery times also depended on the induction anesthetic. Recovery times following barbiturate induction were longer (30 minutes to extubation and 118 minutes to standing), compared to dogs induced with propofol (23 minutes to extubation and 84 minutes to standing).

Cardiac arrhythmias were monitored by ECG. Dexmedetomidine-treated dogs were more frequently observed with at least one incidence of arrhythmia compared to saline controls. The most commonly observed arrhythmias were bradycardia, 1st and 2nd degree AV block, and sinus arrest. Other less frequently observed arrhythmias included ventricular premature complexes (VPCs), supraventricular premature complexes, 3rd degree AV block, and sinus pause.

Adverse events included bradycardia, tachycardia, VPCs, vomiting, diarrhea, urinary incontinence, and self trauma **(see ADVERSE REACTIONS).**

The results of the preanesthesia field study demonstrate that dexmedetomidine provided anesthetic dose-sparing, sedation, and analgesia during procedures conducted under general anesthesia.

Feline sedation/analgesia field study: Dexmedetomidine hydrochloride was evaluated in a masked, controlled, multiple site field study, using parallel treatment groups. Effectiveness was evaluated in 242 client-owned cats, ranging in age between 6 months and 17 years, and in size between 2.3 and 9.6 kg (5 and 21 lbs). Cats admitted to veterinary clinics for various procedures requiring restraint, sedation, and/or analgesia were randomized to treatment group and given dexmedetomidine (122 cats) or xylazine (120 cats) once by IM injection. Procedures performed using dexmedetomidine included dental care, radiography, minor superficial surgery, otitis treatment, blood or urine sample collection, tattooing, microchip placement, and grooming.

Sedation and analgesia occurred within 5 to 15 minutes and peak effects were observed 30 minutes after dexmedetomidine. The procedure was easily performed in 91% of cats beginning 30 minutes after dexmedetomidine. Sedative and analgesic effects waned by three hours after dexmedetomidine.

Signs of sedation were deeper for cats receiving dexmedetomidine compared to those receiving xylazine. No clinically relevant differences were observed between dexmedetomidine and xylazine with respect to analgesia or physiological variables. Heart rate, respiratory rate, and rectal temperature decreased. Bradycardia was observed within 5 to 15 minutes and heart rates of ≤70 beats/minute were seen in 18% of cats. The most commonly observed arrhythmias assessed with ECG were atrioventricular dissociation and escape rhythms, followed by a few incidences of premature complexes and one incidence of atrioventricular block. Oxygen saturation, mucous membrane color, capillary refill time, pulse character, respiratory depth and pattern, and response of the animal to injection were clinically satisfactory. All cats recovered from changes induced by dexmedetomidine.

Ninety-seven adverse events were reported after dexmedetomidine. The most frequently reported adverse reactions included vomiting (70), urinary incontinence (6), hypersalivation (4), involuntary defecation (4), hypothermia (2), and diarrhea (2) **(see ADVERSE REACTIONS).**

The results of this field study demonstrate that dexmedetomidine produces satisfactory levels of sedation and analgesia for clinical examinations and procedures, minor surgical procedures, and minor dental procedures.

Feline preanesthesia field study: The use of dexmedetomidine as a preanesthetic was evaluated in a masked, controlled, multi-site field study, using parallel treatment groups. Effectiveness was evaluated in 182 healthy, client-owned cats, between 12 weeks and 16 years of age, weighing 2.10 to 18.8 lbs (0.9 kg to 8.5 kg). Preanesthetic/induction drug regimens included saline/ketamine, dexmedetomidine/ketamine, saline/propofol, and dexmedetomidine/propofol. All cats were intubated prior to the procedure. Inhalant anesthesia (isoflurane) was added during longer procedures (>15 minutes) and could be added during shorter procedures if the veterinarian deemed it necessary. Procedures included ovariohysterectomy, orchiectomy, onychectomy, and dental cleaning.

Dexmedetomidine IM administered at 40 mcg/kg prior to induction with ketamine resulted in a significantly higher proportion of cats that were successfully intubated compared to saline (success rates of 89.5% and 10.7%, respectively).

Cats preanesthetized with dexmedetomidine IM required 48.9% less propofol for successful intubation compared to cats that received saline. Inhalant anesthetic requirements were 35-44% less for dexmedetomidine preanesthetized cats. Recovery times following ketamine and propofol induction averaged 36 and 38 minutes to extubation and 161 and 131 minutes to standing, respectively for dexmedetomidine-treated groups.

Dexmedetomidine (followed by ketamine or propofol) resulted in the following ECG abnormalities (in decreasing order of frequency): sinus bradycardia, sinus arrhythmia, 1st degree atrioventricular (AV) block, long QT interval, sinus pauses, ventricular premature depolarizations, 2nd degree AV block, escape beats/rhythms, and supraventricular premature depolarizations. Dexmedetomidine-treated cats had a lower mean heart rate, respiratory rate, and body temperature compared to saline controls continuing through the recovery period.

Sixty-six adverse events were reported after dexmedetomidine. The most frequently reported adverse events were: vomiting (32), pale mucous membranes (20), decreased body temperature (4), and retching (4). **(See ADVERSE REACTIONS).**

ANIMAL SAFETY: Canine safety study: In the multiple dose safety study, dexmedetomidine was administered at 0, 1, 3 or 5 times (×) the recommended IV and IM doses on 3 consecutive days to a total of 36 healthy, young beagles. Two additional groups were given a 3× dose of dexmedetomidine (IV or IM) followed by three 1× doses of the reversal agent, atipamezole, every 30 minutes. This was repeated for a total of 3 days. No deaths occurred during the study.

1× dose group: At the recommended dose, sedation lasted less than 3 hours. During sedation, muscle twitches occurred intermittently, and decreases in temperature, respiratory rate and heart rate were observed in all animals. A slow pupil response to light was seen transiently about 15 minutes after dosing in one of twelve dogs. Second degree atrioventricular (AV) blocks were observed in one of twelve dogs.

3× dose group: At 3 times the recommended dose, the duration of sedation was between two and eight hours. During sedation, muscle twitches occurred, and temperature, respiratory rate, and heart rate decreased in all dogs. The pupillary light reflex was transiently decreased for up to 90 minutes in four of twelve dogs. Vomiting was seen in two of twelve dogs. One

dog experienced first and second degree AV blocks; second degree AV block was observed in three of twelve dogs. Elevated concentrations of alanine aminotransferase (ALT) were observed in one dog, without histological changes to the liver.

5× dose group: At 5 times the recommended dose, the duration of sedation was between four and eight hours. Muscle twitches, decreases in temperature, respiratory rates, and heart rates were seen in all dogs. No pupil response was noted in six of twelve dogs (IV) for up to 1.5 hours; decreased transient pupillary light reflex was seen for up to 60 minutes in two of twelve dogs (IM). Vomiting was seen in one of twelve dogs. First and second degree AV blocks were observed in one of twelve dogs. Elevated concentrations of ALT were observed in 3 of 12 dogs, without histological changes to the liver.

Dexmedetomidine demonstrated dose dependent effects related to its pharmacology when administered IV or IM to healthy dogs at doses up to five times the recommended dose

Canine safety study with an anticholinergic: In another laboratory safety study, one of three doses of an IM anticholinergic drug or saline was administered 10 minutes before, at the same time, or 15 minutes after 500 mcg/m^2 IM dexmedetomidine. The anticholinergic drug was given for the prevention or treatment of dexmedetomidine-induced reduction in heart rate. In a crossover design, 18 dogs were used in a total of 72 trials, to evaluate the safety of dexmedetomidine used with an anticholinergic drug.

Dogs were instrumented for the accumulation of continuous ECG data. The following arrhythmias were recorded during the study (some dogs experienced more than one arrhythmia).

Table 8: Arrhythmias recorded during the canine laboratory safety study*

Type of arrhythmia	Number of dogs (of 18)
Second degree AV block	18
Supraventricular tachycardia (SVT) or SVPCs	16
Ventricular escape beats	16
Ventricular premature contractions	14
Third degree AV block	6
Idioventricular rhythm	1
Paroxysmal VT	1
Ventricular bigeminy; SVPCs; pulse alternans	1
Junctional escape beat	1

*** Table does not relate arrhythmias to the presence or absence of anticholinergic**

The occurrence of arrhythmias was not related to the presence or absence of the anticholinergic drug. Arrhythmias were transient (although frequent over time in some dogs), returning toward baseline levels within 55 minutes after dexmedetomidine. No dogs required treatment related to these arrhythmias, and none of these arrhythmias persisted or adversely affected the overall clinical status of any dog in the study.

Dexmedetomidine without anticholinergic: Without the anticholinergic drug, and in addition to arrhythmias, dexmedetomidine produced clinically relevant sedation accompanied by a statistically significant reduction in heart rate, respiratory rate, cardiac output, pulmonary arterial temperature, and mixed venous oxygen tension. A statistically significant increase in arterial blood pressure, pulmonary capillary wedge pressure, central venous pressure, and systemic vascular resistance was noted. No dogs experienced hypotension. Dexmedetomidine tended to increase pulmonary vascular resistance. Dexmedetomidine alone had no statistically significant effect on mean pulmonary arterial pressure, arterial pH, arterial carbon dioxide tension, and arterial oxygen tension.

Dexmedetomidine plus anticholinergic: Either of the two higher anticholinergic doses was effective in the prevention or treatment of the dexmedetomidine-induced reduction in heart rate. Anticholinergic (higher doses) given after dexmedetomidine caused marked increases in the occurrence of various cardiac arrhythmias, especially second degree AV block. When the higher doses of anticholinergic drug were given at the same time or 15 minutes after dexmedetomidine, large increases in heart rate ($p<0.01$) and blood pressure ($p<0.05$) were seen. Increases were dose related; the highest anticholinergic dose elicited more frequent arrhythmias and larger increases in heart rate and blood pressure.

In conclusion, moderate doses of anticholinergic drug given prior to dexmedetomidine performed best for the prevention of dexmedetomidineinduced reduction of heart rate in dogs. The routine use of anticholinergics given simultaneously with, or after dexmedetomidine, is not recommended.

Feline safety study: In a multiple dose safety study, dexmedetomidine hydrochloride was administered intramuscularly (IM) at 1×, 3×, and 5× (40, 120, and 200 mcg/kg) the recommended dose of 40 mcg/kg on 3 consecutive days to healthy cats, 6 to 8 months old. A control group received the product vehicle as a placebo (0×). No mortality was observed. The depth and duration of sedation was dose dependent, lasting approximately 2 hours in the 1× group, 2 to 4 hours in the 3× group, and greater than 8 hours in the 5× group. The lowest recorded individual heart rate was 60 beats/minute and occurred in the 5× dose group (2 cats). Cardiac arrhythmias characterized by isolated junctional escape complexes with episodes of junctional escape rhythm were observed during periods of low heart rate or following sinus pauses in all dexmedetomidine dose groups. In most cases the arrhythmia was no longer observed after 1 to 2 hours. Atrioventricular block was not observed. Incidences of arrhythmias were not related to dose; however, more cats were affected by cardiac arrhythmias on the third day of treatment, compared to the first two days of the study. The decrease in respiratory rate, but not the duration, was dose dependent. The rectal temperature decreased in all dexmedetomidine-treated groups, with the lowest temperatures in the 5× group at 8 hours on all three days. Two cats vomited (40 and 120 mcg/kg). Corneal opacity was noted in all dexmedetomidine-dose groups, was transient, related to dose and duration of sedation, and was attributed to lack of lubrication with decreased blinking during sedation. Hematology and blood chemistry were unaffected by treatment. Injection site tolerance was good, with mild inflammatory lesions representative of the IM injection procedure. Gross and histological examination of all other tissues did not reveal any abnormalities related to dexmedetomidine hydrochloride administration.

Dexmedetomidine demonstrated dose dependent effects related to its pharmacology when administered IM to healthy cats at doses up to five times the recommended dose.

Feline acute tolerance study: IM dexmedetomidine hydrochloride was administered once at 10× (400 mcg/kg) the recommended dose of 40 mcg/kg to 3 female and 3 male 7 month old cats. No mortality was observed. Sedation was observed within 15 minutes of dosing and lasted for at least 4 hours with full recovery noted between 8 and 24 hours after dosing. Transient observations of corneal dehydration and opacity, miosis, pale skin and gingiva, salivation, and watery ocular discharge were observed in some animals. Vomiting was observed 7 to 11 hours after dosing in all but one animal. Decreases in heart rate accompanied by prolonged PQ and QT intervals were most pronounced 2 to 4 hours after dosing. No atrioventricular (AV) blocks or escape rhythms were noted. In one cat, incidental and reversible premature junctional complexes were seen at 1 and 2 hours after dosing which were considered secondary to bradycardia. Slightly lower respiratory rate and reduced rectal temperature were observed 4 to 8 hours after dosing. Observations had returned to normal by 24 hours after dosing. Mild inflammatory lesions observed histologically at the injection site were representative of the IM injection procedure. No treatment related changes were observed in hematology. Mild elevations in some clinical ALT, AST, and CK, were observed 24 hours after dosing, with a trend towards recovery by 48 hours. Total protein, albumin and globulin levels were slightly lowered in one cat 48 hours after dosing.

STORAGE INFORMATION: Store at controlled room temperature 20°C to 25°C (68°-77°F). Protect from freezing. Use within 28 days of first puncture.

HOW SUPPLIED: DexmedVet™ 0.5 mg/mL is supplied in 10-mL, multidose vials containing 0.5 mg of dexmedetomidine hydrochloride per mL.

REFERENCES:

1. Ko JCH, Fox SMF, Mandsager RE. Effects of preemptive atropine administration on incidence of medetomidine-induced bradycardia in dogs. J Am Vet Med Assoc 2001; 218:52-58.
2. Alibhai HIK, Clarke KW, Lee YH, et al. Cardiopulmonary effects of combinations of medetomidine hydrochloride and atropine sulphate in dogs. Vet Rec 1996; 138:11-13.
3. Short, CE. Effects of anticholinergic treatment on the cardiac and respiratory systems in dogs sedated with medetomidine. Vet Rec 1991; 129:310-313.
4. Hikasa Y, Akiba T, Iino Y et al. Central alpha-adrenoceptor subtypes involved in the emetic pathway in cats. Eur J Pharmacol 1992; 229:241-251.

TAKE TIME. OBSERVE LABEL DIRECTIONS.

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816.
Contact No: 1-844-227-6687
(1-844-2-CRONUS)
Made in India
July 2023
Approved by FDA under ANADA # 200-752

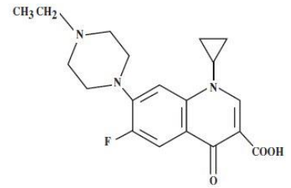
ENROPRO™ 22.7 (ENROFLOXACIN) ANTIBACTERIAL INJECTABLE SOLUTION 2.27%

For Dogs Only

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian. **Federal law prohibits the extralabel use of this drug in food-producing animals.**

DESCRIPTION: Enrofloxacin is a synthetic chemotherapeutic agent from the class of the quinolone carboxylic acid derivatives. It has antibacterial activity against a broad spectrum of Gram negative and Gram positive bacteria (See Tables I and II). Each mL of injectable solution contains: enrofloxacin 22.7 mg, n-butyl alcohol 30 mg, potassium hydroxide for pH adjustment and water for injection, q.s.

CHEMICAL NOMENCLATURE AND STRUCTURAL FORMULA:
1-cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.



ACTIONS:
Microbiology: Quinolone carboxylic acid derivatives are classified as DNA gyrase inhibitors. The mechanism of action of these compounds is very complex and not yet fully understood. The site of action is bacterial gyrase, a synthesis promoting enzyme. The effect on *Escherichia coli* is the inhibition of DNA synthesis through prevention of DNA supercoiling. Among other things, such compounds lead to the cessation of cell respiration and division. They may also interrupt bacterial membrane integrity.[1]

Enrofloxacin is bactericidal, with activity against both Gram negative and Gram positive bacteria. The minimum inhibitory concentrations (MICs) were determined for a series of 37 isolates representing 9 genera of bacteria from natural infections in dogs, selected principally because of resistance to one or more of the following antibiotics: ampicillin, cephalothin, colistin, chloramphenicol, erythromycin, gentamicin, kanamycin, penicillin, streptomycin, tetracycline, triple sulfa and sulfa/trimethoprim. The MIC values for enrofloxacin against these isolates are presented in Table I. Most strains of these organisms were found to be susceptible to enrofloxacin *in vitro* but the clinical significance has not been determined for some of the isolates.

The susceptibility of organisms to enrofloxacin should be determined using enrofloxacin 5 mcg disks. Specimens for susceptibility testing should be collected prior to the initiation of enrofloxacin therapy.

TABLE I — MIC Values for Enrofloxacin Against Canine Pathogens (Diagnostic laboratory isolates, 1984)

Organisms	Isolates	MIC Range (mcg/mL)
Bacteroides spp	2	2
Bordetella bronchiseptica	3	0.125-0.5
Brucella canis	2	0.125-0.25
Clostridium perfringens	1	0.5
Escherichia coli	4	≤0.016-0.031
Klebsiella spp.	10	0.031-0.5
Proteus mirabilis	6	0.062-0.125
Pseudomonas aeruginosa	4	0.5-8
Staphylococcus spp.	5	0.125

The inhibitory activity on 120 isolates of seven canine urinary pathogens was also investigated and is listed in Table II.

TABLE II — MIC Values for Enrofloxacin Against Canine Urinary Pathogens (Diagnostic laboratory isolates, 1985)

Organisms	Isolates	MIC Range (mcg/ mL)
E. coli	30	0.06-2.0
P. mirabilis	20	0.125-2.0
K. pneumoniae	20	0.06-0.5
P. aeruginosa	10	1.0-8.0
Enterobacter spp	10	0.06-1.0
Staph. (coag. +)	20	0.125-0.5
Strep. (alpha hemol.)	10	0.5-8.0

Distribution in the Body: Enrofloxacin penetrates into all canine tissues and body fluids. Concentrations of drug equal to or greater than the MIC for many pathogens (See Tables I, II and III) are reached in most tissues by two hours after dosing at 2.5 mg/kg and are maintained for 8-12 hours after dosing. Particularly high levels of enrofloxacin are found in urine. A summary of the body fluid/tissue drug levels at 2 to 12 hours after dosing at 2.5 mg/kg is given in Table III.

TABLE III — Body Fluid/Tissue distribution of Enrofloxacin in Dogs
Single Oral Dose = 2.5 mg/kg (1.13 mg/lb)

	Post-treatment Enrofloxacin Levels Canine (n=2)	
Body Fluids (mcg/mL)	**2 Hr.**	**8 Hr.**
Urine	43.05	55.35
Eye Fluids	0.53	0.66
Whole Blood	1.01	0.36
Plasma	0.67	0.33
Tissues (mcg/g) Hematopoietic System		
Liver	3.02	1.36
Spleen	1.45	0.85
Bone Marrow	2.10	1.22
Lymph Node	1.32	0.91
Urogenital System		
Kidney	1.87	0.99
Bladder Wall	1.36	0.98
Testes	1.36	1.10
Prostate	1.36	2.20
Uterine Wall	1.59	0.29
Gastrointestinal and Cardiopulmonary Systems		
Lung	1.34	0.82
Heart	1.88	0.78
Stomach	3.24	2.16
Small Intestine	2.10	1.11
Other		
Fat	0.52	0.40
Skin	0.66	0.48
Muscle	1.62	0.77
Brain	0.25	0.24
Mammary Gland	0.45	0.21
Feces	1.65	9.97

Pharmacokinetics: In dogs, the absorption and elimination characteristics of the oral formulation are linear (plasma concentrations increase proportionally with dose) when enrofloxacin is administered at up to 11.5 mg/kg, twice daily.[2] Approximately 80% of the orally administered dose enters the systemic circulation unchanged. The eliminating organs, based on the drug's body clearance time, can readily remove the drug with no indication that the eliminating mechanisms are saturated. The primary route of excretion is via the urine. The absorption and elimination characteristics beyond this point are unknown. Saturable absorption and/or elimination processes may occur at greater doses. When saturation of the absorption process occurs, the plasma concentration of the active moiety will be less than predicted, based on the concept of dose proportionality.

Following an oral dose in dogs of 2.5 mg/kg (1.13 mg/lb), enrofloxacin reached 50% of its maximum serum concentration in 15 minutes and peak serum level was reached in one hour. The elimination half-life in dogs is approximately 2½ -3 hours at that dose.

A graph indicating the mean serum levels following a dose of 2.5 mg/kg (1.13 mg/lb) in dogs (oral and intramuscular) is shown in Figure 1.

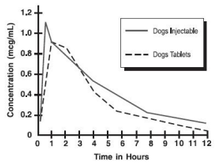


Figure 1 - Serum Concentrations of Enrofloxacin Following a Single Oral or Intramuscular Dose at 2.5 mg/kg in Dogs.

Breakpoint: Based on pharmacokinetic studies of enrofloxacin in dogs after a single oral administration of 2.5 mg enrofloxacin/kg BW (i.e. half of the lowest-end single daily dose range) and the data listed in Tables I and II, the following breakpoints are recommended for canine isolates.

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 21	≤ 0.5	Susceptible(S)
18 - 20	1	Intermediate (I)
≤ 17	≥ 2	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable plasma levels. A report of "intermediate" is a technical buffer and isolates falling into this category should be retested. Alternatively the organism may be successfully treated if the infection is in a body site where drug is physiologically concentrated. A report of "resistant" indicates that the achievable drug concentrations are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms for both standardized disk diffusion assays and standardized dilution assays. The 5 µg enrofloxacin disk should give the following zone diameters and enrofloxacin powder should provide the following MIC values for reference strains.

QC strain	MIC (µg/mL)	Zone Diameter (mm)
E. coli ATCC 25922	0.008 - 0.03	32 - 40
P. aeruginosa ATCC 27853	1-4	15 - 19
S. aureus ATCC 25923		27-31
S. aureus ATCC 29213	0.03 - 0.12	

INDICATIONS: EnroPro™ 22.7 Injectable Solution is indicated for the management of diseases in dogs associated with bacteria susceptible to enrofloxacin.

EFFICACY CONFIRMATION: Clinical efficacy was established in dermal infections (wounds and abscesses) associated with susceptible strains of *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* and *Staphylococcus intermedius*; respiratory infections (pneumonia, tonsillitis, rhinitis) associated with susceptible strains of *Escherichia coli* and *Staphylococcus aureus*; and urinary cystitis associated with susceptible strains of *Escherichia coli, Proteus mirabilis*, and *Staphylococcus aureus*.

CONTRAINDICATIONS: Enrofloxacin is contraindicated in dogs known to be hypersensitive to quinolones.

Based on the studies discussed under the section on Animal Safety Summary, the use of enrofloxacin is contraindicated in small and medium breeds of dogs during the rapid growth phase (between 2 and 8 months of age). The safe use of enrofloxacin has not been established in large and giant breeds during the rapid growth phase. Large breeds may be in this phase for up to one year of age and the giant breeds for up to 18 months. In clinical field trials utilizing a daily oral dose of 5.0 mg/kg, there were no reports of lameness or joint problems in any breed. However, controlled studies with histological examination of the articular cartilage have not been conducted in the large or giant breeds.

ADVERSE REACTIONS: No drug-related side effects were reported in 122 clinical cases treated with enrofloxacin injectable solution followed by enrofloxacin tablets at 5.0 mg/kg per day.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet, contact Cronus Pharma LLC at 1-844-227-6687 or 1-844-2-CRONUS. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

ANIMAL SAFETY SUMMARY: Adult dogs receiving enrofloxacin orally at a daily dosage rate 52 mg/kg for 13 weeks had only isolated incidences of vomition and inappetence. Adult dogs receiving the tablet formulation for 30 consecutive days at a daily treatment of 25 mg/kg did not exhibit significant clinical signs nor were there effects upon the clinical chemistry, hematological or histological parameters. Daily doses of 125 mg/kg for up to 11 days induced vomition, inappetence, depression, difficult locomotion and death while adult dogs receiving 50 mg/kg/day for 14 days had clinical signs of vomition and inappetence.

Adult dogs dosed intramuscularly for three treatments at 12.5 mg/kg followed by 57 oral treatments at 12.5 mg/kg, all at 12 hour intervals, did not exhibit either significant clinical signs or effects upon the clinical chemistry, hematological or histological parameters.

Oral treatment of 15 to 28 week old growing puppies with daily dosage rates of 25 mg/kg has induced abnormal carriage of the carpal joint and weakness in the hindquarters. Significant improvement of clinical signs is observed following drug withdrawal. Microscopic studies have identified lesions of the articular cartilage following 30 day treatments at either 5, 15 or 25 mg/kg in this age group. Clinical signs of difficult ambulation or associated cartilage lesions have not been observed in 29 to 34 week old puppies following daily treatments of 25 mg/kg for 30 consecutive days nor in 2 week old puppies with the same treatment schedule.

Tests indicated no effect on circulating microfilariae or adult heart-worms (*Dirofilaria immitis*) when dogs were treated at a daily dosage rate of 15 mg/kg for 30 days. No effect on cholinesterase values was observed.

No adverse effects were observed on reproductive parameters when male dogs received 10 consecutive daily treatments of 15 mg/kg/day at 3 intervals (90, 45 and 14 days) prior to breeding or when female dogs received 10 consecutive daily treatments of 15 mg/kg/day at 4 intervals; between 30 and 0 days prior to breeding, early pregnancy (between 10th & 30th days), late pregnancy (between 40th & 60th days), and during lactation (the first 28 days).

DRUG INTERACTIONS: Concomitant therapy with other drugs that are metabolized in the liver may reduce the clearance rates of the quinolone and the other drug.

Enrofloxacin has been administered to dogs at a daily dosage rate of 10 mg/kg concurrently with a wide variety of other health products including anthelmintics (praziquantel, febantel), insecticides (pyrethrins), heartworm preventatives (diethylcarbamazine) and other antibiotics (ampicillin, gentamicin sulfate, penicillin). No incompatibilities with other drugs are known at this time.

WARNINGS: For use in animals only. The use of this product in cats may result in Retinal Toxicity. Keep out of reach of children.

Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation persists following ocular or dermal exposure. Individuals with a history of hypersensitivity to quinolones should avoid this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight.

PRECAUTION: Quinolone-class drugs should be used with caution in animals with known or suspected Central Nervous System (CNS) disorders. In such animals, quinolones have, in rare instances, been associated with CNS stimulation which may lead to convulsive seizures.

Quinolone-class drugs have been associated with cartilage erosions in weight-bearing joints and other forms of arthropathy in immature animals of various species.

The use of fluoroquinolones in cats has been reported to adversely affect the retina. Such products should be used with caution in cats.

DOSAGE AND ADMINISTRATION: EnroPro™ 22.7 Injectable Solution may be used as the initial dose at 2.5 mg/kg. It should be administered intramuscularly (IM) as a single dose, followed by initiation of enrofloxacin tablet therapy.

EnroPro™ 22.7 Injectable Solution may be administered as follows:

Weight of Animal	EnroPro™ 22.7 Injectable Solution* 2.5 mg/kg
9.1 kg (20 lb)	1.00 mL
27.2 kg (60 lb)	3.00 mL

*The initial EnroPro™ 22.7 Injectable administration should be followed 12 hours later by initiation of enrofloxacin tablet therapy.

The lower limit of the dose range was based on efficacy studies in dogs where enrofloxacin was administered at 2.5 mg/kg twice daily. Target animal safety and toxicology studies were used to establish the upper limit of the dose range and treatment duration.

STORAGE: Protect from direct sunlight. Do not freeze. Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F).

Use within 90 days of first puncture and puncture a maximum of 20 times for 20 mL fill and 50 times for 50 mL fill. Any product remaining after specified punctures or more than 90 days after initial puncture should be discarded.

HOW SUPPLIED:

Code Number	EnroPro™ 22.7 Injectable Solution 22.7 mg/mL Vial Size
NDC 69043-047-02	20 mL
NDC 69043-047-05	50 mL

EnroPro™ is the registered trademarks of Cronus Pharma LLC

REFERENCES:

1. Dougherty, T.J. and Saukkonen, J.J. Membrane Permeability Changes Associated with DNA Gyrase Inhibitors in *Escherichia coli*. Antimicrob.Agents and Chemoth., V. 28, Aug. 1985: 200-206.

2. Walker, R.D., *et al*. Pharmacokinetic Evaluation of Enrofloxacin Administered Orally to Healthy Dogs. Am.J. Res., V. 53, No. 12, Dec. 1992: 2315-2319.3.

Approved by FDA under ANADA # 200-764

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816
Contact No: 1-844-227-6687
(1-844-2-CRONUS)

Made in India
Revised: 08/2024
PC047-02

TAKE TIME. OBSERVE LABEL DIRECTIONS.

ENROPRO™ SILVER OTIC (ENROFLOXACIN/SILVER SULFADIAZINE) ANTIBACTERIAL-ANTIMYCOTIC EMULSION

For Ototopical Use In Dogs

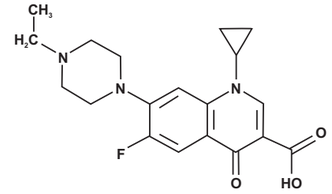
CAUTION: Federal Law restricts this drug to use by or on the order of a licensed veterinarian. **Federal law prohibits the extralabel use of this drug in food-producing animals.**

DESCRIPTION: Each milliliter of EnroPro™ Silver Otic contains: enrofloxacin 5 mg (0.5% w/v), silver sulfadiazine (SSD) 10 mg (1.0% w/v), benzyl alcohol (as a preservative) and cetostearyl alcohol (as a stabilizer) in a purified water emulsion, sorbitan monostearate, polysorbate 60, and medium chain triglycerides. The active ingredients are delivered via a physiological carrier (a nonirritating emulsion).

CHEMICAL NOMENCLATURE AND STRUCTURE:

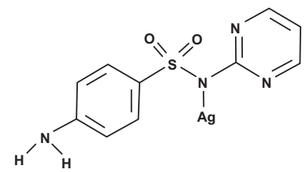
Enrofloxacin

1-Cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1, 4-dihydro-4-oxo-3-quinolinecarboxylic acid.



Silver Sulfadiazine

Benzenesulfonamide, 4-amino-N-2-pyrimidinyl-monosilver



ACTIONS: Enrofloxacin, a 4-fluoroquinolone compound, is bactericidal with activity against a broad spectrum of both Gram negative and Gram positive bacteria. Fluoroquinolones elicit their bactericidal activities through interactions with two intracellular enzymes, DNA gyrase (DNA topoisomerase II) and DNA topoisomerase IV, which are essential for bacterial DNA transcription, synthesis and replication. It is believed that fluoroquinolones actively bind with bacterial DNA:ENZYME complexes and thereby inhibit the essential processes catalyzed by the enzymes (DNA supercoiling and chromosomal decatenation).[1] The ultimate outcome of the fluoroquinolone intervention is DNA fragmentation and bacterial cell death.[2,3]

Silver sulfadiazine (SSD) is synthesized from silver nitrate and sodium sulfadiazine.[4] This compound has a wide spectrum of antimicrobial activity against Gram negative and Gram positive bacteria and is also an effective antimycotic.[5,6] SSD suppresses microbial growth through inhibition of DNA replication and modification of the cell membrane.

MICROBIOLOGY: In clinical field trials, enrofloxacin/silver sulfadiazine otic demonstrated elimination or reduction of clinical signs associated with otitis externa and *in vitro* activity against cultured organisms. enrofloxacin/silver sulfadiazine otic is effective when used as a treatment for canine otitis externa associated with one or more of the following organisms: *Malassezia pachydermatis, coagulase-positive Staphylococcus spp., Pseudomonas aeruginosa, Enterobacter spp., Proteus mirabilis, Streptococci spp., Aeromonas hydrophila, Aspergillus spp., Klebsiella pneumoniae, and Candida albicans.*

In vitro assays, such as disk-diffusion and agar/broth-dilution, are used to determine the susceptibilities of microbes to antimicrobial therapies. Results of agar/broth-dilution assays are reported as a Minimal Inhibitory Concentration (MIC) which represents the lowest antimicrobial concentration, expressed in µg/mL, capable of inhibiting the growth of a pathogenic microorganism. MICs are used in conjunction with pharmacokinetics to predict the in *vivo* efficacy of systemically administered antimicrobials. Topical administration of enrofloxacin/silver sulfadiazine otic to an exudate and debris-free canal, however, will generally result in local antimicrobial concentrations that greatly exceed serum and tissue levels resulting from systemic therapy. Therefore, when using enrofloxacin/silver sulfadiazine otic as a treatment for canine otitis externa, interpret susceptibility data cautiously.

INDICATIONS: EnroPro™ Silver Otic is indicated as a treatment for canine otitis externa complicated by bacterial and fungal organisms susceptible to enrofloxacin and/or silver sulfadiazine (see Microbiology section).

EFFECTIVENESS: Due to its combination of active ingredients, enrofloxacin/silver sulfadiazine otic provides antimicrobial therapy against bacteria and fungi (which includes yeast) commonly encountered in cases of canine otitis externa.

The effectiveness of enrofloxacin/silver sulfadiazine otic was evaluated in a controlled, double-blind, multi-site clinical trial. One hundred and sixty-nine dogs (n=169), with naturally occurring active otitis externa participated in the study. The presence of active disease was verified by aural cytology, microbial culture and otoscopy/clinical scoring. Qualified cases were randomly assigned to either enrofloxacin/silver sulfadiazine otic treatment (n=113) or to a comparable placebo-based regimen (n=56). Treatments were administered twice daily for up to 14 days. Assessment of effectiveness was based on continued resolution of clinical signs 3 to 4 days following administration of the last dose.

At study conclusion, enrofloxacin/silver sulfadiazine otic was found to be a significantly more effective treatment for canine otitis externa than the placebo regimen. Based on the scoring system used to assess treatment response, therapeutic success occurred in 67% of enrofloxacin/silver sulfadiazine otic-treated infections compared to 14% with placebo (r-value[2] 0.001) after 14 days of treatment.

CONTRAINDICATIONS: EnroPro™ Silver Otic is contraindicated in dogs with suspected or known hypersensitivity to quinolones and/or sulfonamides.

HUMAN WARNINGS: Not for human use. Keep out of the reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation develops or persists following ocular or dermal exposures. Individuals with a history of hypersensitivity to quinolone compounds or antibacterials should avoid handling this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight.

PRECAUTIONS: The use of EnroPro™ Silver Otic in dogs with perforated tympanic membranes has not been evaluated. Therefore, the integrity of the tympanic membrane should be evaluated before administering this product. If hearing or vestibular dysfunction is noted during the course of treatment, discontinue use of EnroPro™ Silver Otic.

Quinolone-class drugs should be used with caution in animals with known or suspected Central Nervous System (CNS) disorders. In such animals, quinolones have, in rare instances, been associated with CNS stimulation which may lead to convulsive seizures.

Quinolone-class drugs have been associated with cartilage erosions in weightbearing joints and other forms of arthropathy in immature animals of various species.

The safe use of EnroPro™ Silver Otic in dogs used for breeding purposes, during pregnancy, or in lactating bitches, has not been evaluated.

ADVERSE REACTIONS: During clinical trials, 2 of 113 (1.7%) dogs exhibited reactions that may have resulted from treatment with enrofloxacin/silver sulfadiazine otic. Both cases displayed local hypersensitivity responses of the aural epithelium to some component within the enrofloxacin/silver sulfadiazine otic formulation. The reactions were characterized by acute inflammation of the ear canal and pinna.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the SDS, contact Cronus Pharma LLC at 1-844-227-6687 or 1-844-2-CRONUS. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae. SAFETY:

General Safety Study: In a target animal safety study, enrofloxacin/silver sulfadiazine otic was administered in both ears of 24 clinically normal beagle dogs at either recommended or exaggerated dosages: 10, 30 or 50 drops applied twice daily for 42 consecutive days. A control group of 8 beagle dogs was treated by administering 50 drops of vehicle in one ear twice daily for 42 consecutive days, with the contralateral ear untreated. Erythema was noted in all groups, including both treated and untreated ears in the controls, which resolved following termination of treatment.

Oral Safety Study: In order to test safety in case of ingestion, enrofloxacin/silver sulfadiazine otic was administered, twice daily for 14 consecutive days, to the dorsum of the tongue and to the left buccal mucosa of 6 clinically normal dogs. No adverse local or systemic reactions were reported.

DOSAGE AND ADMINISTRATION: Shake well before each use. Tilt head so that the affected ear is presented in an upward orientation. Administer a sufficient quantity of EnroPro™ Silver Otic to coat the aural lesions and the external auditory canal.

As a general guide, administer 5-10 drops per treatment in dogs weighing 35 lbs. or less and 10-15 drops per treatment in dogs weighing more than 35 lbs. Following treatment, gently massage the ear so as to ensure complete and uniform distribution of the medication throughout the external ear canal. Apply twice daily for a duration of up to 14 days.

STORAGE: Store between 4° and 25°C (40 - 77°F). Store in an upright position. Do not store in direct sunlight.

HOW SUPPLIED: EnroPro™ Silver Otic (enrofloxacin/silver sulfadiazine)

Size	Presentation
15 mL	White LDPE bottle with HDPE cap and dropper
30 mL	White LDPE bottle with HDPE cap and dropper

REFERENCES:

1. Hooper DC and Wolfson JS. Mechanisms of quinolone action and bacterial killing in quinolone antimicrobial agents. Washington DC, American Society for Microbiology, 2nd ed., 1993: 53-75.
2. Gootz TD and Brightly KE. Fluoroquinolone antibacterial: mechanism of action, resistance and clinical aspects. Medicinal Research Reviews 1996:16 (5): 433-486.
3. Drlica K and Zhoa X. DNA gyrase, topoisomerase IV and the 4-quinolones. Microbiology and Molecular Biology Reviews 1997: 61(3): 377-392.
4. Fox CL. Silver sulfadiazine: a new topical therapy for Pseudomonas in burns. Archives of Surgery 1968: 96:184-188.
5. Wlodkowski TJ and Rosenkranz HS. Antifungal activity of silver sulfadiazine. Lancet 1973: 2:739-740.
6. Schmidt A. In vitro activity of climbazole, clotrimazole and silver sulfadiazine against isolates of Malassezia pachy-dermatis. J of Vet Medicine Series B 1997: 44:193-197.

Approved by FDA under ANADA # 200-782

TAKE TIME.
OBSERVE LABEL
DIRECTIONS.

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816
Contact No: 1-844-227-6687
(1-844-2-CRONUS)

Code: TS/DRUGS/24/2009
Made in India
Revised: 04/2024
PC056-00

METHYLPREDNISOLONE TABLETS, USP

For Oral Use in Dogs and Cats Only

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
DESCRIPTION: Methylprednisolone, a potent glucocorticoid and anti-inflammatory agent, is a synthetic 6-methyl derivative of prednisolone. It has a greater anti-inflammatory potency than prednisolone and is less likely to induce sodium and water retention. Its advantage over the older corticoids lies in its ability to achieve equal anti-inflammatory effect with a lower dose, while at the same time enhancing the split between anti-inflammatory and mineralocorticoid activities. [1, 2, 3] Each tablet contains 1mg, 2mg or 4mg of methylprednisolone.

ACTIONS: Glucocorticoids exert a regulatory influence on lymphocytes, erythrocytes and eosinophils of the blood and on the structure and function of lymphoid tissues.[1, 4, 5] A primary feature of the glucocorticoids is their anti-inflammatory activity with minimum sodium and water retention which is often associated with the mineralocorticoids. [1, 2, 3, 4, 5, 6] Glucocorticoids not only inhibit the early phases of the inflammatory process (edema, fibrin deposition, capillary dilation, migration of leukocytes into the inflamed area and phagocytic activity) but also the later manifestations (capillary proliferation, fibroblast proliferation and deposition of collagen). [3, 4, 6] The exact mechanism is not known, but the glucocorticoids obviously suppress normal tissue response to injury and alleviate symptoms from many conditions.[2]

INDICATIONS: The indications are the same as those for other anti-inflammatory steroids and comprise the various collagen, dermal, allergic, ocular, otic and musculoskeletal conditions known to be responsive to the anti-inflammatory corticosteroids. Representative of the conditions in which the use of steroid therapy and the benefits to be derived therefrom have had repeated confirmation in the veterinary literature are:

Dermal conditions, such as non-specific eczema and summer dermatics. [1, 2, 4]

Allergic manifestations, such as acute urticaria, allergic dermatitis, drug and serum reactions, non-specific pruritus, bronchial asthma and pollen sensitivities. [1, 2, 3, 4, 5]

Ocular Conditions, such as iritis, iridocyclitis, secondary glaucoma, uveitis and chlorioretinitis. [1, 3, 4, 5]

Otic Conditions, such as otitis externa. [4]

Musculoskeletal Conditions, such as myositis, rheumatoid arthritis, osteoarthritis and bursitis. [1, 2, 3, 4, 5]

Various chronic or recurrent diseases of unknown etiology such as ulcerative colitis and nephrosis. [1, 2, 3, 5]

In acute adrenal insufficiency, methylprednisolone may be effective because of its ability to correct the defect in carbohydrate metabolism and relieve the impaired diuretic response to water, characteristic of primary or secondary adrenal insufficiency. However, because this agent lacks significant mineralocorticoid activity, hydrocortisone sodium succinate or cortisone should be used when salt retention is indicated.

CONTRAINDICATIONS: Do not use in viral infections. Methylprednisolone, like prednisolone, is contraindicated in animals with arrested tuberculosis, peptic ulcer, acute psychoses, corneal ulcer and Cushingoid syndrome. The presence of diabetes, osteoporosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, congestive heart failure, renal insufficiency and active tuberculosis necessitates carefully controlled use. Some of the above conditions occur only rarely in dogs and cats but should be kept in mind.

WARNING: Because of its inhibitory effect on fibroplasia, methylprednisolone may mask the signs of infection and enhance dissemination of the infecting organism. Hence all animals receiving methylprednisolone should be watched for evidence of intercurrent infection. Should infection occur, it must be brought under control by use of appropriate antibacterial measures or administration of methylprednisolone should be discontinued.

Not for human use. Clinical and experimental data have demonstrated that corticosteroids administered orally or parenterally to animals may induce the first stage of parturition when administered during the last trimester of pregnancy and may precipitate premature parturition followed by dystocia, fetal death, retained placenta and metritis.

Additionally, corticosteroid administered to dogs, rabbits and rodents during pregnancy have produced cleft palate. Other congenital anomalies including deformed forelegs, phocomella and anasarca have been reported in offspring of dogs which received corticosteroids during pregnancy.

PRECAUTIONS:
Methylprednisolone, like prednisolone and other adrenocortical steroids, is a potent therapeutic agent influencing the biochemical behavior of most, if not all, tissues of the body. Because this anti-inflammatory steroid manifests little sodium-retaining activity, the usual early sign of cortisone or hydrocortisone overdosage (i.e., increase in body weight due to fluid retention) is not a reliable index of overdosage. Hence, recommended dosage levels should not be exceeded, and all animals receiving methylprednisolone should be under close medical supervision. All precautions pertinent to the use of prednisolone apply to methylprednisolone. Moreover, the veterinarian should endeavor to keep informed of current studies with methylprednisolone as they are reported in the veterinary literature.

Use of corticosteroids, depending on dose, duration and specific steroid, may result in inhibition of endogenous steroid production following drug withdrawal. In patients presently receiving or recently withdrawn from systemic corticosteroid treatments, therapy with a rapid acting corticosteroid should be considered in usually stressful situations.

ADVERSE REACTIONS: Methylprednisolone is similar to prednisolone in regard to kinds of side effects and metabolic alterations to be anticipated when treatment is intensive or prolonged. In animals with diabetes mellitus, use of methylprednisolone may be associated with an increase in the insulin requirement. Negative nitrogen balance may occur, particularly in animals that require protracted maintenance therapy; measures to counteract persistent nitrogen loss include a high protein intake and the administration, when indicated, of a suitable anabolic agent. Excessive loss of potassium, like excessive retention of sodium, is not likely to be induced by effective maintenance doses of methylprednisolone. However these effects should be kept in mind and the usual regulatory measures employed as indicated. Ecchymotic manifestations, **while not noted during the clinical evaluation in dogs and cats,** may occur. If such reactions do occur and are serious, reduction in dosage or discontinuance of methylprednisolone therapy may be indicated. Concurrent use of daily oral supplements of ascorbic acid may be of value in helping to control ecchymotic tendencies.

Side effects, such as SAP and SGPT enzyme elevations, weight loss, anorexia, polydipsia and polyuria have occurred following the use of synthetic corticosteroids in dogs. Vomiting and diarrhea (occasionally bloody) have been observed in dogs and cats. Cushing's syndrome in dogs has been reported in association with prolonged or repeated steroid therapy.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet, contact Cronus Pharma LLC at 1-844-227-6687 and 1-844-2-CRONUS. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

DOSAGE AND ADMINISTRATION: The keystone of satisfactory therapeutic management with methylprednisolone, as with its steroid predecessors, is individualization of dosage in reference to the severity of the disease, the anticipated duration of steroid therapy and the animal's threshold or tolerance for steroid excess. The prime objective of steroid therapy should be achieve a satisfactory degree of control with a minimum effective daily dose.

The dosage recommendations are suggested **average total daily doses and are intended as guides.** As with other orally administered corticosteroids, the total daily dose of methylprednisolone tablets should be given in equally divided doses. The initial suppressive dose level is continued until a satisfactory clinical response is obtained, a period usually of 2 to 7 days in the case of musculoskeletal diseases, allergic conditions affecting the skin or respiratory tract and ocular inflammatory diseases. If a satisfactory response is not obtained in 7 days, re-evaluation of the case to confirm the original diagnosis should be made. As soon as a satisfactory clinical response is obtained, the daily dose should be reduced gradually, either to termination of treatment in the case of acute conditions (e.g., seasonal asthma, dermatitis, acute ocular inflammations) or to the minimal effective maintenance dose level in the case of chronic conditions (e.g., rheumatoid arthritis). In chronic conditions, and in rheumatoid arthritis especially, it is important that the reduction in dosage from initial to maintenance dose levels be accomplished slowly. The maintenance dose level should be adjusted from time to time as required by fluctuation in the activity of the disease and the animal's general status. Accumulated experience has shown that the long-term benefits to be gained from continued steroid maintenance are probably greater the lower the maintenance dose level. In rheumatoid arthritis in particular, maintenance steroid therapy should be at the lowest possible level.

IMPORTANT: In the therapeutic management of animals with chronic diseases, such as rheumatoid arthritis, methylprednisolone should be regarded as a highly valuable adjunct, to be used in conjunction with but not as a replacement for standard therapeutic measures.

RECOMMENDED DOSAGE SCHEDULE: Average total daily doses for dogs and cats are as follows:
5 to 15 lb body weight.....2 mg
15 to 40 lb body weight.....2 to 4 mg
40 to 80 lb body weight.....4 to 8 mg
Use half tablets as needed to achieve the desired dose
The total daily dose should be given in doses, 6 to 10 hours apart.

HOW SUPPLIED: Methylprednisolone tablets, USP 1mg, 2mg are yellow round shaped scored tablets available in bottles of 100 and 500. Methylprednisolone tablets, USP 4mg are yellow oval shaped scored tablets available in bottles of 100 and 500.

Each 1mg tablet contains 1mg methylprednisolone, USP.
Each 2mg tablet contains 2mg methylprednisolone, USP.
Each 4mg tablet contains 4mg methylprednisolone, USP.
Split tablets should be used within 90 days.
Store at controlled room temperature 20° to 25°C (68° to 77°F).

REFERENCES: 1. Osol, A., ed., 1980. Remington's Pharmaceutical Sciences, 16th Edition. Mack Publishing Company, Easton, PA. 898-901, 908.
2. Martindale, The Extra pharmacopoeia, 27th Edition, 1977. The Pharmaceutical Press, London, England. 389-396, 424-425
3. Gilman, A.G., L.S. Goodman and A. Gilman, eds., 1980. The Pharmacological Basis of Therapeutics, 6th Edition. Macmillan Publishing Co., Inc., New York. NY. 1470-1496.
4. Booth, N.H and L.E McDonald, eds., 1982. Veterinary Pharmacology and Therapeutics, 5th Edition. The Iowa State University Press, Ames, IA. 553-570.
5. Dipalma, J.R., ed., 1976. Basic Pharmacology in Medicine, McGraw-Hill, Inc., St. Louis, MO 328-337.
6. Kirk, R.W., ed., 1980. Current Veterinary Therapy VII, Small Animal Practice. W.B Saunders Company. Philadelphia, PA. 497-500, 992-994.

KEEP OUT OF REACH OF CHILDREN: Approved by FDA under NADA # 135-771
Code: 4206162/TS/DRUGS/2023

TAKE TIME.
OBSERVE LABEL
DIRECTIONS.

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816
Contact No: 1-844-227-6687
(1-844-2-CRONUS)

Code: 4206162/TS/DRUGS/2023
Made in India
May 2023
PC040-00

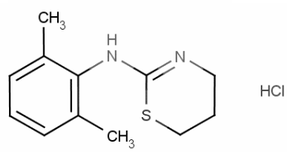
ANASED® EQUINE INJECTION (XYLAZINE INJECTION) 100 mg/mL

For intravenous (IV) or intramuscular (IM) use in horses only

---

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian
Sedative.

DESCRIPTION:



Xylazine is an alpha$_2$-adrenoreceptor agonist with sedative properties. The chemical name for Xylazine is 2-(2,6-dimethylphenylamino)-4H-5,6-dihydro-1,3-thiazine. The formula for the hydrochloride salt is $C_{12}H_{16}N_2S$.HCl. Xylazine Injection is a clear, colorless solution. Each mL of sterile Xylazine Injection contains xylazine HCl equivalent to 100 mg xylazine base; 0.9 mg methylparaben and 0.1 mg propylparaben as preservatives; 6.12 mg sodium citrate dihydrate; water for injection, q.s. hydrochloric acid and/or sodium citrate dihydrate may also be used as necessary to adjust the pH.

INDICATIONS: AnaSed® Equine Injection should be used in horses when it is desirable to produce a state of sedation. It has been successfully used when conducting various diagnostic, orthopedic and dental procedures of short duration. It may also be used as a preanesthetic to local or general anesthesia.

DOSAGE AND ADMINISTRATION: For intravenous or intramuscular administration in horses. The recommended dosage for intravenous (IV) administration is 0.5 mL/100 lbs body weight (0.5 mg/lb). The recommended dosage for intramuscular (IM) administration is 1 mL/100lbs body weight (1 mg/lb).

Following the administration of AnaSed® Equine Injection the horse should be allowed to rest quietly until the full effect has been reached. These dosages produce a state of sedation which is usually maintained for 1 to 2 hours (See Clinical Pharmacology).

Preanesthetic to local anesthesia: At the recommended dosages AnaSed® Equine Injection may be used in conjunction with local anesthetics, such as procaine and lidocaine.

Preanesthetic to general anesthesia: At the recommended dosages AnaSed® Equine Injection produces an additive effect to central nervous system depressants, such as sodium pentobarbital, sodium thiopental and sodium thiamylal. Accordingly, the dosage of such products should be reduced and administered to the desired effect. Generally, 1/3 to 1/2 of the calculated dosage of the barbiturates will be needed to produce a surgical plane of anesthesia. Postanesthetic or emergence excitement has not been observed in horses preanesthetized with AnaSed® Equine Injection.

AnaSed® Equine Injection has been successfully used as a preanesthetic agent for sodium pentobarbital, sodium thiopental, sodium thiamylal, nitrous oxide, ether, halothane, guaifenesin and methoxyflurane anesthesia.
CONTRAINDICATIONS: AnaSed® Equine Injection should not be used in conjunction with neuroleptics or tranquilizers.

WARNINGS:

USER SAFETY WARNINGS:
Not for use in humans. Keep out of reach of children.

Avoid skin, eye or mucosal contact. Use caution while handling and using filled syringes.

Absorption of the active ingredients is possible following exposure via the skin, eye or mucosa. In case of accidental eye exposure, flush eyes with water for 15 minutes, remove contact lenses then continue to flush. In case of accidental skin exposure, wash with soap and water and remove contaminated clothing. If symptoms occur, seek the advice of a physician.

In case of accidental oral intake or self-injection, seek medical advice immediately and show the package insert to the physician. DO NOT DRIVE as sedation, loss of consciousness, and changes in blood pressure may occur.

Persons with cardiovascular disease (for example, hypertension or ischemic heart disease) should take special precautions to avoid any exposure to this product.

Pregnant women should exercise special caution to avoid exposure. Uterine contractions and decreased fetal blood pressure may occur after accidental systemic exposure.

Persons with known hypersensitivity to any of the ingredients should avoid contact with AnaSed® Equine Injection.

Caution should be exercised when handling sedated animals. Handling or any other sudden stimuli, including noise, may cause a defense reaction in an animal that appears to be heavily sedated.

Note to Physician: AnaSed® Equine Injection contains xylazine HCl, an alpha2-adrenoceptor agonist. Symptoms after absorption or accidental self-injection may include dose-dependent sedation, respiratory depression, bradycardia, tachycardia, and hypotension.

ANIMAL SAFETY WARNINGS: Intracarotid arterial injection should be avoided. As with many drugs, including tranquilizers, immediate and violent seizures followed by collapse may result from inadvertent administration into the carotid artery. Although the reaction with AnaSed® Equine Injection is usually transient and the recovery rapid and complete, special care should be taken to assure that the needle is in the jugular vein rather than the carotid artery.

OTHER WARNINGS: Do not use in horses intended for human consumption.

PRECAUTIONS: Debilitated horses with depressed respiration, cardiac disease, renal or liver impairment, shock or any other stress conditions should be carefully monitored whenever AnaSed® Equine Injection is administered.

AnaSed® Equine Injection produces an additive effect to central nervous system depressants and caution should be taken when administering barbiturate compounds in conjunction with AnaSed® Equine Injection. Barbiturates should be administered at a reduced dosage and to the desired effect, and when injected intravenously should be given slowly.

Arrhythmias resulting in partial atrioventricular (AV) blocks and bradycardia are transient changes which may occur, but that can be counteracted to a large degree by the administration of atropine prior to or following AnaSed® Equine Injection (xylazine injection).

Analgesic effect is variable and depth should be carefully determined prior to surgical or clinical procedures. Variability of analgesia occurs most frequently at the distal extremities of horses. In spite of sedation, the practitioner should proceed with caution since defense reactions may not be diminished.

Horses under the influence of AnaSed® Equine Injection are particularly sensitive to noise and care should be taken accordingly to avoid risk of injury. Sedation for transport is most successful if actual transport is initiated after full effect of the drug has been obtained and the horse's stability maintained in the standing position.

ADVERSE REACTIONS: The deep sedation produced by AnaSed® Equine Injection is characterized by lowering of the head, drooping of the eyelids and lower lip and a marked reluctance to move. Most horses given AnaSed® Equine Injection sweat around the ears and poll region and may seem particularly sensitive to sharp auditory stimuli during the recovery period. The respiratory and pulse rate are reduced as in natural sleep. Transient changes in the conductivity of the cardiac muscle (resulting in partial AV blocks), bradycardia, decreased cardiac output and a rise in arterial blood pressure may occur following intravenous administration.

CONTACT INFORMATION: To report suspected adverse reactions, for technical assistance, or to obtain a copy of the Safety Data Sheet (SDS), call Cronus Pharma at (844) 227-6687. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae

CLINICAL PHARMACOLOGY: Xylazine Injection is pharmacologically classified as a non-narcotic sedative. The drug causes sedation by acting upon alpha-adrenergic receptors in the brain to prevent the release of norepinephrine. Xylazine Injection also produces muscle relaxation by inhibiting the intraneural transmission of impulses in the central nervous system.

Deep sedation develops in the horse within 10 to 15 minutes after intramuscular injection, and within 3 to 5 minutes following intravenous administration.

Deep sedation lasts 15 to 20 minutes, while a sleep-like state, the depth of which is dose-dependent, is usually maintained for 1 to 2 hours following intramuscular administration of the drug at the recommended dosage. Recovery is complete with 30-40 minutes following intravenous injection.

In animals under the influence of Xylazine Injection, the respiratory and pulse rates are reduced as in a natural sleep. The intramuscular injection of Xylazine produces only negligible effects on the cardiovascular and respiratory systems. However, intravenous administration in the horse may cause transient changes in the conductivity of the cardiac muscle, evidenced by partial AV blocks, bradycardia, decreased cardiac output and a rise in arterial blood pressure. These actions are transient and can be counteracted to a large degree by the administration of atropine prior to or following Xylazine Injection. Xylazine Injection has no effect on blood clotting time or other hematologic parameters.

TARGET ANIMAL SAFETY: Xylazine Injection is tolerated in horses at 10 times the recommended dosage, however doses of this magnitude produce muscle tremors and long periods of sedation.

HOW SUPPLIED: AnaSed® Equine Injection, 100 mg/mL, is available in 50 mL multiple-dose vials.

STORAGE: Store at up to 25 °C (77 °F). Use within 28 days of first puncture.

Approved by FDA under NADA # 140-442

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816
Contact No: 1-844-227-6687
(1-844-2-CRONUS)

Code: 4206162/TS/DRUGS/2023
Made in India
Revised: 09/2024
PC043-02

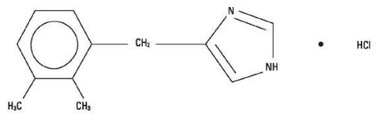
DETOMISED™ (10 mg/mL)

Sedative and Analgesic For Use in Horses Only Sterile solution

---

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
DESCRIPTION: DetomiSed™ is a synthetic alpha-2 adrenoreceptor agonist with sedative and analgesic properties. The chemical name is 1H imidazole, 4-[(2,3-dimethylphenyl) methyl]-hydrochloride and the generic name is detomidine hydrochloride. It is a white, crystalline, water-soluble substance having a molecular weight of 222.7. The molecular formula is $C_{12}H_{14}N_2$.HCl.

CHEMICAL STRUCTURE:



Each mL of DetomiSed™ contains 10.0 mg detomidine hydrochloride, 1.0 mg methyl paraben, 5.9 mg sodium chloride, and water for injection, q.s.

CLINICAL PHARMACOLOGY: DetomiSed™, a non-narcotic sedative and analgesic, is a potent α2-adrenoreceptor agonist which produces sedation and superficial and visceral analgesia which is dose dependent in its depth and duration. Profound lethargy and a characteristic lowering of the head with reduced sensitivity to environmental stimuli (sounds, etc.) are seen with detomidine. A short period of incoordination is characteristically followed by immobility and a firm stance with front legs well spread. The analgesic effect is most readily seen as an increase in the pain threshold at the body surface. Sensitivity to touch is little affected and in some cases may actually be enhanced.

With detomidine administration, heart rate is markedly decreased, blood pressure is initially elevated, and then a steady decline to normal is seen. A transient change in the conductivity of the cardiac muscle may occur, as evidenced by partial atrioventricular (AV) and sinoauricular (SA) blocks. This change in the conductivity of the cardiac muscle may be prevented by IV administration of atropine at 0.02 mg/kg of body weight.

No effect on blood clotting time or other hematological parameters was encountered at dosages of 20 or 40 mcg/kg of body weight. Respiratory responses include an initial slowing of respiration within a few seconds to 1 to 2 minutes after administration, increasing to normal within 5 minutes. An initial decrease in tidal volume is followed by an increase.

INDICATIONS: DetomiSed™ is indicated for use as a sedative and analgesic to facilitate minor surgical and diagnostic procedures in mature horses and yearlings. It has been used successfully for the following: to calm fractious horses, to provide relief from abdominal pain, to facilitate bronchoscopy, bronchoalveolar lavage, nasogastric intubation, nonreproductive rectal palpations, suturing of skin lacerations, and castrations. Additionally, an approved, local infiltration anesthetic is indicated for castration.

CONTRAINDICATIONS: DetomiSed™ should not be used in horses with pre-existing AV or SA block, with severe coronary insufficiency, cerebrovascular disease, respiratory disease, or chronic renal failure. Intravenous potentiated sulfonamides should not be used in anesthetized or sedated horses as potentially fatal dysrhythmias may occur.

Information on the possible effects of detomidine hydrochloride in breeding horses is limited to uncontrolled clinical reports; therefore, this drug is not recommended for use in breeding animals.

WARNINGS: DO NOT USE IN HORSES INTENDED FOR HUMAN CONSUMPTION. NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.

HUMAN SAFETY INFORMATION: Care should be taken to assure that detomidine hydrochloride is not inadvertently ingested as safety studies have indicated that the drug is well absorbed when administered orally. Standard ocular irritation tests in rabbits using the proposed market formulation have shown detomidine hydrochloride to be nonirritating to eyes. Primary dermal irritation tests in guinea pigs using up to 5 times the proposed market concentration of detomidine hydrochloride on intact and abraded skin have demonstrated that the drug is nonirritating to skin and is apparently poorly absorbed dermally. However, in accordance with prudent clinical procedures, exposure of eyes or skin should be avoided and affected areas should be washed immediately if exposure does occur. As with all injectable drugs causing profound physiological effects, routine precautions should be employed by practitioners when handling and using loaded syringes to prevent accidental self-injection.

PRECAUTIONS: Before administration, careful consideration should be given to administering DetomiSed™ to horses approaching or in endotoxic or traumatic shock, to horses with advanced liver or kidney disease, or to horses under stress from extreme heat, cold, fatigue, or high altitude. Protect treated horses from temperature extremes. Some horses, although apparently deeply sedated, may still respond to external stimuli. Routine safety measures should be employed to protect practitioners and handlers. Allowing the horse to stand quietly for 5 minutes before administration and for 10 to 15 minutes after injection may improve the response to DetomiSed™.

DetomiSed™ is a potent α2-agonist, and extreme caution should be exercised in its use with other sedative or analgesic drugs for they may produce additive effects.

When using any analgesic to help alleviate abdominal pain, a complete physical examination and diagnostic work-up are necessary to determine the etiology of the pain.

ADVERSE REACTIONS: Occasional reports of anaphylactic-like reactions have been received, including 1 or more of the following: urticaria, skin plaques, dyspnea, edema of the upper airways, trembling, recumbency, and death. **The use of epinephrine should be avoided since epinephrine may potentiate the effects of α2-agonists.** Reports of mild adverse reactions have resolved uneventfully without treatment. Severe adverse reactions should be treated symptomatically. As with all α2-agonists, the potential for isolated cases of hypersensitivity exist, including paradoxical response (excitation).

CONTACT INFORMATION: To report suspected adverse drug experience, for technical assistance or to obtain a copy of the Safety Data Sheet, contact Cronus Pharma LLC at 1-844-227-6687 or 1-844-2-CRONUS.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae

SIDE EFFECTS: Horses treated with DetomiSed™ exhibit hypertension. Bradycardia routinely occurs 1 minute after injection. The relationship between hypertension and bradycardia is consistent with an adaptive baroreceptor response to the increased pressure and inconsistent with a primary drug-induced bradycardia. Piloerection, sweating, salivation, and slight muscle tremors are frequently seen after administration. Partial transient penis prolapse may be seen. Partial AV and SA blocks may occur with decreased heart and respiratory rates. Urination typically occurs during recovery at about 45 to 60 minutes posttreatment, depending on dosage. Incoordination or staggering is usually seen only during the first 3 to 5 minutes after injection, until animals have secured a firm footing.

Because of continued lowering of the head during sedation, mucus discharges from the nose and, occasionally, edema of the head and face may be seen. Holding the head in a slightly elevated position generally prevents these effects.

OVERDOSAGE: Detomidine hydrochloride is tolerated in horses at up to 200 mcg/kg of body weight (10 times the low dosage and 5 times the high dosage). In safety studies in horses, detomidine hydrochloride at 400 mcg/kg of body weight administered daily for 3 consecutive days produced microscopic foci of myocardial necrosis in 1 of 8 horses.

DOSAGE AND ADMINISTRATION:
For Sedation: Administer DetomiSed™ IV or IM at the rates of 20 or 40 mcg detomidine hydrochloride per kg of body weight (0.2 or 0.4 mL of DetomiSed™ per 100 kg or 220 lb), depending on the depth and duration of sedation required. Onset of sedative effects should be reached within 2 to 4 minutes after IV administration and 3 to 5 minutes after IM administration. Twenty mcg/kg will provide 30 to 90 minutes of sedation and 40 mcg/kg will provide approximately 90 minutes to 2 hours of sedation.

For Analgesia: Administer DetomiSed™ IV at the rates of 20 or 40 mcg detomidine hydrochloride per kg of body weight (0.2 or 0.4 mL of DetomiSed™ per 100 kg or 220 lb), depending on the depth and duration of analgesia required. Twenty mcg/kg will usually begin to take effect in 2 to 4 minutes and provide 30 to 45 minutes of analgesia. The 40 mcg/kg dose will also begin to take effect in 2 to 4 minutes and provide 45 to 75 minutes of analgesia.

For Both Sedation and Analgesia: Administer DetomiSed™ IV at the rates of 20 or 40 mcg detomidine hydrochloride per kg of body weight (0.2 or 0.4 mL of DetomiSed™ per 100 kg or 220 lb), depending on the depth and duration of sedation and analgesia required.

Before and after injection, the animal should be allowed to rest quietly.

STORAGE: Store at (20° to 25°C) in the absence of light; excursions permitted to 40°C. Use contents within 28 days of first puncture.

HOW SUPPLIED: DetomiSed™ is supplied in 5 mL and 20 mL multi-dose vials.

NDC 69043-057-95, 5 mL vial in package of one.
NDC 69043-057-02, 20 mL vial in package of one.

Approved by FDA under ANADA # 200-611

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816
Contact No: 1-844-227-6687
(1-844-2-CRONUS)

Code: 4206162/TS/DRUGS/2023
Made in India
Revised: 1/2025

FLUNINE™ (FLUNIXIN MEGLUMINE INJECTION) 50 MG/ML

Only for Intravenous Use in Beef and Dairy Cattle. Not for Use in Dry Dairy Cows and Veal Calves. For Intravenous and Intramuscular Use in Horses.

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Each milliliter of Flunine™ (flunixin meglumine injection) contains 50 mg flunixin (equivalent to 83 mg flunixin meglumine), 0.1 mg edetate disodium, 2.5 mg sodium formaldehyde sulfoxylate, 4.0 mg diethanolamine, 207.2 mg propylene glycol; 5.0 mg phenol as preservative, hydrochloric acid, water for injection qs.

PHARMACOLOGY: Flunixin meglumine is a potent, non-narcotic, nonsteroidal, analgesic agent with anti-inflammatory and antipyretic activity. It is significantly more potent than pentazocine, meperidine, and codeine as an analgesic in the rat yeast paw test.

Horse: Flunixin is four times as potent on a mg-per-mg basis as phenylbutazone as measured by the reduction in lameness and swelling in the horse. Plasma half-life in horse serum is 1.6 hours following a single dose of 1.1 mg/kg. Measurable amounts are detectable in horse plasma at 8 hours postinjection.

Cattle: Flunixin meglumine is a weak acid (pKa=5.82)[1] which exhibits a high degree of plasma protein binding (approximately 99%).[2] However, free (unbound) drug appears to readily partition into body tissues (V_{ss} predictions range from 297 to 782 mL/kg.[2-5] Total body water is approximately equal to 570 mL/kg).[6] In cattle, elimination occurs primarily through biliary excretion.[7] This may, at least in part, explain the presence of multiple peaks in the blood concentration/time profile following IV administration.[2]

In healthy cattle, total body clearance has been reported to range from 90 to 151 mL/kg/hr.[2-5] These studies also report a large discrepancy between the volume of distribution at steady state (V_{ss}) and the volume of distribution associated with the terminal elimination phase (V_{β}). This discrepancy appears to be attributable to extended drug elimination from a deep compartment.[8] The terminal half-life has been shown to vary from 3.14 to 8.12 hours.[2-5]

Flunixin persists in inflammatory tissues[9] and is associated with anti-inflammatory properties which extend well beyond the period associated with detectable plasma drug concentrations.[4,9] These observations account for the counterclockwise hysteresis associated with flunixin's pharmacokinetic/pharmacodynamic relationships.[10]

Therefore, prediction of drug concentrations based upon the estimated plasma terminal elimination half-life will likely underestimate both the duration of drug action and the concentration of drug remaining at the site of activity.

INDICATIONS:

Horse: Flunine™ Injection (flunixin meglumine) is recommended for the alleviation of inflammation and pain associated with musculoskeletal disorders in the horse. It is also recommended for the alleviation of visceral pain associated with colic in the horse.

Cattle: Flunine™ Injection (flunixin meglumine) is indicated for the control of pyrexia associated with bovine respiratory disease, endotoxemia and acute bovine mastitis. Flunine™ is also indicated for the control of inflammation in endotoxemia.

DOSE AND ADMINISTRATION: USE WITHIN 28 DAYS OF FIRST PUNCTURE AND PUNCTURE A MAXIMUM OF 10 TIMES FOR 100 ML FILL, 25 TIMES FOR 250 ML FILL AND 50 TIMES FOR 500 ML FILL. WHEN USING A DRAW-OFF SPIKE, DISCARD ANY PRODUCT REMAINING IN THE VIAL IMMEDIATELY AFTER USE.

Horse: The recommended dose for musculoskeletal disorders is 0.5 mg per pound (1 mL/100 lbs) of body weight once daily. Treatment may be given by intravenous or intramuscular injection and repeated for up to 5 days. Studies show onset of activity is within 2 hours. Peak response occurs between 12 and 16 hours and duration of activity is 24-36 hours.

The recommended dose for the alleviation of pain associated with equine colic is 0.5 mg per pound of body weight. Intravenous administration is recommended for prompt relief. Clinical studies show pain is alleviated in less than 15 minutes in many cases. Treatment may be repeated when signs of colic recur. During clinical studies approximately 10% of the horses required one or two additional treatments. The cause of colic should be determined and treated with concomitant therapy.

Cattle: The recommended dose for control of pyrexia associated with bovine respiratory disease and endotoxemia and control of inflammation in endotoxemia, is 1.1 to 2.2 mg/kg (0.5 to 1 mg/lb; 1 to 2 mL per 100 lbs) of body weight given by slow intravenous administration either once a day as a single dose or divided into two doses administered at 12-hour intervals for up to 3 days. The total daily dose should not exceed 2.2 mg/kg (1.0 mg/lb) of body weight. Avoid rapid intravenous administration of the drug.

The recommended dose for acute bovine mastitis is 2.2 mg/kg (1 mg/lb; 2 ml per 100 lbs) of body weight given once by intravenous administration.

CONTRAINDICATIONS:

Horse: There are no known contraindications to this drug when used as directed. Intra-arterial injection should be avoided. Horses inadvertently injected intra-arterially can show adverse reactions. Signs can be ataxia, incoordination, hyperventilation, hysteria, and muscle weakness. Signs are transient and disappear without antidotal medication within a few minutes. Do not use in horses showing hypersensitivity to flunixin meglumine.

Cattle: NSAIDs inhibit production of prostaglandins which are important in signaling the initiation of parturition. The use of flunixin can delay parturition and prolong labor which may increase the risk of stillbirth. Do not use Flunine™ Injection (flunixin meglumine) within 48 hours of expected parturition. Do not use in animals showing hypersensitivity to flunixin meglumine. Use judiciously when renal impairment or gastric ulceration are suspected.

RESIDUE WARNINGS: Cattle must not be slaughtered for human consumption within 4 days of the last treatment. Milk that has been taken during treatment and for 36 hours after the last treatment must not be used for food. Not for use in dry dairy cows. A withdrawal period has not been established for this product in preruminating calves. Do not use in calves to be processed for veal. Not for use in horses intended for food. Approved only for intravenous administration in cattle. Intramuscular administration has resulted in violative residues in the edible tissues of cattle sent to slaughter.

PRECAUTIONS: As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal and renal toxicity. Sensitivity to drug-associated adverse effects varies with the individual patient. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction.

Since many NSAIDs possess the potential to induce gastrointestinal ulceration, concomitant use of Flunine™ Injection (flunixin meglumine) with other anti-inflammatory drugs, such as other NSAIDs and corticosteroids, should be avoided or closely monitored.

Horse: The effect of Flunine™ Injection (flunixin meglumine) on pregnancy has not been determined. Studies to determine activity of Flunine™ when administered concomitantly with other drugs have not been conducted. Drug compatibility should be monitored closely in patients requiring adjunctive therapy.

Cattle: Do not use in bulls intended for breeding, as reproductive effects of Flunine™ Injection (flunixin meglumine) in these classes of cattle have not been investigated. NSAIDs are known to have potential effects on both parturition (See Contraindications) and the estrous cycle. There may be a delay in the onset of estrus if flunixin is administered during the prostaglandin phase of the estrous cycle. NSAIDs are known to have the potential to delay parturition through a tocolytic effect. The use of NSAIDs in the immediate post-partum period may interfere with uterine involution and expulsion of fetal membranes. Cows should be monitored carefully for placental retention and metritis if Flunine™ is used within 24 hours after parturition.

SAFETY:

Horse: A 3-fold intramuscular dose of 1.5 mg/lb of body weight daily for 10 consecutive days was safe.

No changes were observed in hematology, serum chemistry, or urinalysis values. Intravenous dosages of 0.5 mg/lb daily for 15 days; 1.5 mg/lb daily for 10 days; and 2.5 mg/lb daily for 5 days produced no changes in blood or urine parameters. No injection site irritation was observed following intramuscular injection of the 0.5 mg/lb recommended dose. Some irritation was observed following a 3-fold dose administered intramuscularly.

Cattle: No flunixin-related changes (adverse reactions) were noted in cattle administered a 1× (2.2 mg/kg; 1.0 mg/lb) dose for 9 days (three times the maximum clinical duration). Minimal toxicity manifested itself at moderately elevated doses (3× and 5×) when flunixin was administered daily for 9 days, with occasional findings of blood in the feces and/or urine. Discontinue use if hematuria or fecal blood are observed.

ADVERSE REACTIONS: In horses, isolated reports of local reactions following intramuscular injection, particularly in the neck, have been received. These include localized swelling, sweating, induration, and stiffness. In rare instances in horses, fatal or nonfatal clostridial infections or other infections have been reported in association with intramuscular use of flunixin meglumine injection. In horses and cattle, rare instances of anaphylactic-like reactions, some of which have been fatal, have been reported, primarily following intravenous use.

HOW SUPPLIED: Flunine™ Injection (flunixin meglumine), 50 mg/ mL, is available in 100-mL (NDC 69043-055-10), 250-mL (NDC 69043-055-25) and 500-mL (NDC 69043-055-50) multi-dose vials.

Store at or below 25°C (77°F) Do not Freeze. See the in-use directions provided in the DOSE AND ADMINISTRATION section.

REFERENCES:

1. Johansson M, Anler EL. Gas chromatographic analysis of flunixin in equine urine after extractive methylation. J Chromatogr. 1988; 427:55-66.
2. Odensvik K, Johansson M. High-performance liquid chromatography method for determination of flunixin in bovine plasma and pharmacokinetics after single and repeated doses of the drug. Am J Vet Res. 1995; 56:489-495.
3. Anderson KL, Neff-Davis CA, Davis LE, Bass VD. Pharmacokinetics of flunixin meglumine in lactating cattle after single and multiple intramuscular and intravenous administrations. Am J Vet Res. 1990; 51:1464-1467.
4. Odensvik K. Pharmacokinetics of flunixin and its effect on prostaglandin F2α metabolite concentrations after oral and intravenous administration in heifers. J Vet Pharmacol Ther. 1995; 18:254-259.
5. Hardee GE, Smith JA, Harris SJ. Pharmacokinetics of flunixin meglumine in the cow. Res Vet Sci. 1985; 39:110-112.
6. Ruckebusch Y, Phaneuf LP, Dunlop R. Physiology of Small and Large Animals. Chapter 2: "Body Fluid Compartments," Philadelphia, Pa: B.C. Decker; 1991:8-18.
7. Kopcha M, Ahl AS. Experimental uses of flunixin meglumine and phenylbutazone in food-producing animals. J Am Vet Med Assoc. 1989; 194:45-49.
8. Wagner JG. Significance of ratios of different volumes of distribution in pharmacokinetics. Biopharm & Drug Dispos. 1983; 4:263-270.
9. Lees P, Higgins AJ. Flunixin inhibits prostaglandin E2 production in equine inflammation. Res Vet Sci. 1984; 37:347-349.
10. Landoni MF, Cunningham FM, Lees P. Determination of pharmacokinetics and pharmacodynamics of flunixin in calves by use of pharmacokinetic/pharmacodynamic modeling. Am J Vet Res. 1995; 56:786-794.

Approved by FDA under ANADA # 200-781

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816
Contact No: 1-844-227-6687
(1-844-2-CRONUS)

Code: 4206162/TS/DRUGS/2023
Made in India
Revised: 04/2024 PC05-00

TAKE TIME. OBSERVE LABEL DIRECTIONS.

DORAJECT™ (DORAMECTIN INJECTION)

Antiparasitic
1% injectable solution for cattle and swine
10 mg/mL

PRODUCT DESCRIPTION: Doraject™ injectable solution (doramectin injection) is a ready-to-use, colorless to pale yellow, sterile solution containing 1% w/v doramectin (10 mg/mL). In cattle, Doraject™ is formulated to deliver the recommended dosage (200 mcg/kg of body weight) when given by subcutaneous (SC) or intramuscular (IM) injection at the rate of 1 mL/110 lb of body weight. In swine, Doraject™ is formulated to deliver the recommended dosage (300 mcg/kg of body weight) when given by IM injection at the rate of 1 mL/75 lb of body weight.

PRODUCT CHARACTERISTICS: Doraject™ injectable solution is a highly active, broad-spectrum parasiticide for parenteral administration to cattle and swine. It contains doramectin, a novel fermentation-derived macrocyclic lactone. Doramectin is isolated from fermentations of selected strains derived from the soil organism *Streptomyces avermitilis*.

A primary mode of action of macrocyclic lactones is to modulate chloride ion channel activity in the nervous system of nematodes and arthropods. Macrocyclic lactones bind to receptors that increase membrane permeability to chloride ions. This inhibits the electrical activity of nerve cells in nematodes and muscle cells in arthropods and causes paralysis and death of the parasites. In mammals, the neuronal receptors to which macrocyclic lactones bind are localized within the central nervous system (CNS), a site reached by only negligible concentrations of doramectin.

One dose of Doraject™ injectable solution effectively treats and controls a wide range of roundworm and arthropod parasites that impair the health and productivity of cattle and swine.

Studies have demonstrated the safety margin of doramectin injection in cattle and swine. In USA trials, no toxic signs were seen in cattle given up to 25 times the recommended dose, or in swine given up to 10 times the recommended dose. Studies also demonstrated safety in neonatal calves and piglets treated with up to 3 times the recommended dose. In males (bulls and boars) and females (cows and sows during folliculogenesis, implantation, organogenesis, and through gestation), a dose 3 times the recommended dose had no effect on breeding performance.

PRODUCT INDICATIONS:

Cattle: Doraject™ injectable solution is indicated for the treatment and control of the following harmful species of gastrointestinal roundworms, lungworms, eyeworms, grubs (see PRECAUTIONS), sucking lice (see PRECAUTIONS), and mange mites. Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism.

Gastrointestinal Roundworms (adults and fourth stage larvae)
- *Ostertagia ostertagi (including inhibited larvae)*
- *O. lyrata*
- *Haemonchus placei*
- *Trichostrongylus axei*
- *T. colubriformis*
- *T. longispicularis*†
- *Cooperia oncophora*
- *C. pectinata*†
- *C. punctata*
- *C. surnabada (syn. mcmasteri)*
- *Bunostomum phlebotomum*†
- *Strongyloides papillosus*†
- *Oesophagostomum radiatum*
- *Trichuris spp.*[1]

Lungworms (adults and fourth stage larvae)
- *Dictyocaulus viviparus*

Eyeworms (adults)
- *Thelazia spp.*

Grubs (parasitic stages)
- *Hypoderma bovis*
- *H. lineatum*

Sucking Lice
- *Haematopinus eurysternus*
- *Linognathus vituli*
- *Solenopotes capillatus*

Mange Mites
- *Psoroptes bovis*
- *Sarcoptes scabiei*

† *adults*

Doraject™ injectable solution has been proved to effectively control infections and to protect cattle from reinfection with *Cooperia oncophora* and *Haemonchus placei* for 14 days, *Ostertagia ostertagi* for 21 days, and *C. punctata*, *Oesophagostomum radiatum*, and *Dictyocaulus viviparus* for 28 days after treatment.

Swine: Doraject™ injectable solution is indicated for the treatment and control of the following species of gastrointestinal roundworms, lungworms, kidney worms, sucking lice (see PRECAUTIONS), and mange mites. Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism.

Gastrointestinal Roundworms (adults and fourth stage larvae)
- *Ascaris suum*
- *Oesophagostomum dentatum*
- *Oesophagostomum quadrispinulatum*†
- *Strongyloides ransomi*†
- *Hyostrongylus rubidus*†

† *adults*

Lungworms (adults)
- *Metastrongylus spp.*

Kidney Worms (adults)
- *Stephanurus dentatus*

Mange Mites (adults and immature stages)
- *Sarcoptes scabiei var. suis*

Sucking Lice (adults and immature stages)
- *Haematopinus suis*

DOSAGE: *Cattle:* Administer Doraject™ injectable solution (doramectin injection) at the recommended dosage of 200 mcg doramectin per kg (91 mcg/lb) of body weight. Each mL of Doraject™ contains 10 mg of doramectin, 2.5 mg of phenol, and 215 mg of ethyl oleate in a sesame oil vehicle, sufficient to treat 110 lb (50 kg) of body weight.

Body Weight (lb)	Dose (mL)
110	1
220	2
330	3
440	4
550	5
660	6
770	7
880	8
990	9
1,100	10

Swine: Administer Doraject™ injectable solution at the recommended dosage of 300 mcg doramectin per kg (136 mcg/lb) of body weight. Each mL of Doraject™ contains 10 mg of doramectin, 2.5 mg of phenol, and 215 mg of ethyl oleate in a sesame oil vehicle, sufficient to treat 75 lb (34 kg) of body weight.

Body Weight (lb)	Dose (mL)
15	0.2
30	0.4
45	0.6
60	0.8
75	1.0
150	2.0
225	3.0
300	4.0
375	5.0
450	6.0

Do not underdose. Ensure each animal receives a complete dose based on a current body weight. Underdosing may result in ineffective treatment, and encourage the development of parasite resistance.

RECOMMENDED TREATMENT PROGRAM FOR SWINE: To effectively initiate control of mange and sucking lice in swine, it is important to treat all animals in the herd. After initial treatment, use Doraject™ regularly as follows:

Breeding Animals:
Sows: Treat 7–14 days prior to farrowing to minimize exposure of piglets to mites and sucking lice.
Gilts: Treat 7–14 days prior to breeding. Treat 7–14 days prior to farrowing.
Boars: Treat a minimum of 2 times per year.

Feeder Pigs: Treat any new feeder pigs upon arrival at farm or before placement in clean quarters.

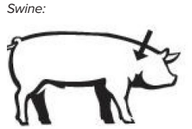
Weaners, Growers, Finishers: Weaners and grow-out/finisher pigs should be treated before placement in clean quarters.
For effective mange elimination, care must be taken to prevent reinfestation from exposure to untreated animals or contaminated facilities.

ADMINISTRATION: Dry, sterile equipment and aseptic procedures should be used when withdrawing and administering Doraject™ (doramectin injection). For multiple treatments either automatic injection equipment or an aspirating needle should be used.

Cattle:

Administer Doraject™ injectable solution by SC or IM route. Injections should be made using a 16 gauge needle for adult cattle or an 18 gauge needle for young animals. Needles 1/2– 3/4" in length are suggested for SC administration. A 1-1/2" needle is suggested for IM administration. SC injections should be administered under the loose skin in front of or behind the shoulder. IM injections should be administered into the muscular region of the neck. Beef Quality Assurance guidelines recommend SC administration as the preferred route.

Swine:



Administer Doraject™ injectable solution by the IM route. Inject in the neck region using an 18 gauge × 1" needle for young animals; a 16 gauge × 1-1/2" needle for sows and boars. To accurately meter doses administered to piglets, use of a tuberculin syringe and 20 gauge × 1" needle is recommended.

WARNINGS: Not for human use. Keep out of reach of children. To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet, contact Cronus Pharma LLC at 1-844-227-6687 (1-844-2-CRONUS).

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

OTHER WARNINGS: Parasite resistance may develop to any dewormer, and has been reported for most classes of dewormers. Treatment with a dewormer used in conjunction with parasite management practices appropriate to the geographic area and the animal(s) to be treated may slow the development of parasite resistance. Fecal examinations or other diagnostic tests and parasite management history should be used to determine if the product is appropriate for the herd prior to the use of any dewormer. Following the use of any dewormer, effectiveness of treatment should be monitored (for example, with the use of a fecal egg count reduction test or another appropriate method). A decrease in a drug's effectiveness over time as calculated by fecal egg count reduction tests may indicate the development of resistance to the dewormer administered. Your parasite management plan should be adjusted accordingly based on regular monitoring.

RESIDUE WARNINGS: *Cattle:* Do not slaughter for human consumption within 35 days of treatment. Not for use in female dairy cattle 20 months of age or older. A withdrawal period has not been established for this product in preruminating calves. Do not use in calves to be processed for veal. *Swine:* Do not slaughter for human consumption within 24 days of treatment.

PRECAUTIONS: Doraject™ has been developed specifically for use in cattle and swine only. This product should not be used in other animal species as severe adverse reactions, including fatalities in dogs, may result.

For SC injection in cattle only. For IM injection in swine and cattle. This product is approved for the treatment and control of sucking lice. For treatment of biting lice in cattle, use of doramectin topical solution is recommended.

Doraject™ is highly effective against all stages of cattle grubs. However, proper timing of treatment is important. For most effective results, cattle should be treated as soon as possible after the end of the heel fly (warble) season.

Destruction of *Hypoderma* larvae (cattle grubs) at the period when these grubs are in vital areas may cause undesirable host-parasite reactions including the possibility of fatalities. Killing *H. lineatum* when it is in the tissue surrounding the gullet may cause bloat; Killing *H. bovis* when it is in the vertebral canal may cause staggering or paralysis. These reactions are not specific to treatment with Doraject™, but can occur with any successful treatment of grubs. Cattle should be treated either before or after these stages of grub development. Consult your veterinarian concerning the proper time for treatment.

Cattle treated with Doraject™ after the end of the heel fly season may be re-treated with Doraject™ during the winter for internal parasites, mange mites, or sucking lice, without danger of grub-related reactions. A planned parasite control program is recommended.

ENVIRONMENTAL SAFETY: Studies indicate that when doramectin comes in contact with the soil, it readily and tightly binds to the soil and becomes inactive over time. Free doramectin may adversely affect fish and certain aquatic organisms. Do not permit water runoff from feedlots to enter streams or ponds. Do not contaminate water by direct application or by the improper disposal of drug containers. Dispose of containers in an approved landfill or by incineration.

As with other avermectins, doramectin is excreted in the dung of treated animals and can inhibit the reproduction and growth of pest and beneficial insects that use dung as a source of food and for reproduction. The magnitude and duration of such effects are species and life-cycle specific. When used according to label directions, the product is not expected to have an adverse impact on populations of dung-dependent insects.

STORAGE CONDITIONS: Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F). Use this product within 90 days of the first puncture and maximum allowable punctures are given in the below table.

If more than the maximum number of punctures is anticipated, the use of multi-dosing equipment is recommended. When using a draw-off spike or needle with bore diameter larger than 16-guage, discard any product remaining in the vial immediately after use.

Fill Volume	Allowable Punctures
100mL	28
250mL	70
500mL	141

HOW SUPPLIED: Doraject™ (doramectin injection) is available in 100-mL, 250-mL, and 500-mL multi-dose, rubber-stoppered glass vials.

Approved by FDA under ANADA # 200-750
Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism.
Not for human use.
Restricted Drug (CA) Use only as directed.

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816.
Contact No: 1-844-227-6687
(1-844-2-CRONUS)
Code: 4206162/TS/DRUGS/2023
Made in India.

December 2023 PC037-00

TAKE TIME.
OBSERVE LABEL
DIRECTIONS.

ENROPRO™ 100 (ENROFLOXACIN) 100 MG/ML ANTIMICROBIAL INJECTABLE SOLUTION

For Subcutaneous Use In Beef Cattle And Non-Lactating Dairy Cattle
For Intramuscular Or Subcutaneous Use In Swine
Not For Use In Female Dairy Cattle 20 Months Of Age Or Older
Or In Calves To Be Processed For Veal

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Federal law prohibits the extra-label use of this drug in food-producing animals.

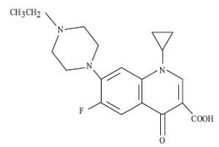
To assure responsible antimicrobial drug use, enrofloxacin should only be used as a second-line drug for

colibacillosis in swine following consideration of other therapeutic options.

DESCRIPTION: EnroPro™ 100 is a sterile, ready-to-use injectable antimicrobial solution that contains enrofloxacin, a broadspectrum antimicrobial agent.

Each mL of EnroPro™ 100 contains 100 mg of enrofloxacin. Excipients are L-arginine base 200 mg, n-butyl alcohol 30 mg, benzyl alcohol (as a preservative) 20 mg and water for injection q.s.

CHEMICAL NOMENCLATURE AND STRUCTURE: 1-cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.



INDICATIONS:
Cattle - Single-Dose Therapy: EnroPro™ 100 is indicated for the treatment of bovine respiratory disease (BRD) associated with Mannheimia haemolytica, Pasteurella multocida, Histophilus somni and Mycoplasma bovis in beef and non-lactating dairy cattle; and for the control of BRD in beef and non-lactating dairy cattle at high risk of developing BRD associated with M. haemolytica, P. multocida, H. somni and M. bovis.

Cattle - Multiple-Day Therapy: EnroPro™ 100 is indicated for the treatment of bovine respiratory disease (BRD) associated with Mannheimia haemolytica, Pasteurella multocida and Histophilus somni in beef and non-lactating dairy cattle.

Swine: EnroPro™ 100 is indicated for the treatment and control of swine respiratory disease (SRD) associated with Actinobacillus pleuropneumoniae, Pasteurella multocida, Haemophilus parasuis, Streptococcus suis, Bordetella bronchiseptica and Mycoplasma hyopneumoniae. EnroPro™ 100 is indicated for the control of colibacillosis in groups or pens of weaned pigs where colibacillosis associated with Escherichia coli has been diagnosed.

DOSAGE AND ADMINISTRATION: EnroPro™ 100 provides flexible dosages and durations of therapy.

EnroPro™ 100 may be administered as a single dose for one day for treatment and control of BRD (cattle), for treatment and control of SRD or for control of colibacillosis (swine), or for multiple days for BRD treatment (cattle). Selection of the appropriate dose and duration of therapy for BRD treatment in cattle should be based on an assessment of the severity of the disease, pathogen susceptibility and clinical response.

Cattle:
Single-Dose Therapy (BRD Treatment): Administer, by subcutaneous injection, a single dose of 7.5-12.5 mg/kg of body weight (3.4-5.7 mL/100 lb).

Multiple-Day Therapy (BRD Treatment): Administer daily, a subcutaneous dose of 2.5-5 mg/kg of body weight (1.1-2.3 mL/100 lb). Treatment should be repeated at 24-hour intervals for three days. Additional treatments may be given on Days 4 and 5 to animals that have shown clinical improvement but not total recovery.

Single-Dose Therapy (BRD Control): Administer, by a subcutaneous injection, a single dose of 7.5 mg/kg of body weight (3.4 ml/100 lb). Examples of conditions that may contribute to calves being at high risk of developing BRD include, but are not limited to, the following:

- Transportation with animals from two or more farm origins.
- An extended transport time with few to no rest stops.
- An environmental temperature changes of ≥30°F during transportation.
- A ≥30°F range in temperature fluctuation within a 24-hour period.
- Exposure to wet or cold weather conditions.
- Excessive shrink (more than would be expected with a normal load of cattle).
- Stressful arrival processing procedures (e.g., castration or dehorning).
- Exposure within the prior 72 hours to animals showing clinical signs of BRD.

Administered dose volume should not exceed 20 mL Per injection site.

Table 1 - EnroPro™ 100 Dose and Treatment Schedule for Cattle *

Weight (lb)	Treatment		Control
	Single-Dose Therapy 7.5 - 12.5 mg/kg Dose Volume (mL)	Multiple-Day Therapy 2.5 - 5.0 mg/kg Dose Volume (mL)	Single-Dose Therapy 7.5 mg/kg Dose Volume (mL)
100	3.5 - 5.5	1.5 - 2.0	3.5
200	7.0 - 11.0	2.5 - 4.5	7.0
300	10.5 - 17.0	3.5 - 6.5	10.5
400	14.0 - 22.5	4.5 - 9.0	14.0
500	17.0 - 28.5	5.5 - 11.5	17.0
600	20.5 - 34.0	7.0 - 13.5	20.5
700	24.0 - 39.5	8.0 - 16.0	24.0
800	27.5 - 45.5	9.0 - 18.0	27.5
900	31.0 - 51.0	10.0 - 20.5	31.0
1000	34.0 - 57.0	11.0 - 23.0	34.0
1100	37.5 - 62.5	12.5 - 25.0	37.5

*Dose volumes have been rounded to the nearest 0.5 mL within the dose range.

Swine: Administer, either by intramuscular or subcutaneous (behind the ear) injection, a single dose of 7.5 mg/kg of body weight (3.4mL/100 lb.) Administered dose volume should not exceed 5 mL per injection site.

For the control of colibacillosis, administration should be initiated within the first 60 days post weaning when clinical signs are present in at least 2% of the animals in the group. If no improvement is noted within 48 hours, the diagnosis should be reevaluated.

Table 2 - EnroPro™ 100 Dose Schedule for Swine

Weight (lb)	Dose Volume (mL)
15	0.5
30	1.0
50	1.7
100	3.4
150	5.1
200	6.8
250	8.5

Dilution of EnroPro™ 100: EnroPro™ 100 may be diluted with sterile water prior to injection. The diluted product should be used within 24 hours. Store diluted solution in amber glass bottles between 4-40°C (36-104°F).

Table 3 - Dilution Schedule*

700	24.0 - 39.5	8.0 - 16.0	24.0
800	27.5 - 45.5	9.0 - 18.0	27.5
900	31.0 - 51.0	10.0 - 20.5	31.0
1000	34.0 - 57.0	11.0 - 23.0	34.0
1100	37.5 - 62.5	12.5 - 25.0	37.5

*Dose volumes have been rounded to the nearest 0.5 mL within the dose range.

Use within 30 days of first puncture and puncture a maximum of 30 times. If more than 30 punctures are anticipated, the use of multi-dosing equipment is recommended. When using a draw-off spike or needle with bore diameter larger than 16-gauge, discard any product remaining in the vial immediately after use.

RESIDUE WARNINGS:
Cattle: Animals intended for human consumption must not be slaughtered within 28 days from the last treatment. This product is not approved for female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or in calves born to these cows. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

Swine: Animals intended for human consumption must not be slaughtered within 5 days of receiving a single-injection dose.

HUMAN WARNINGS: Not for use in humans. Keep out of reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation persists following ocular or dermal exposures. Individuals with a history of hypersensitivity to quinolones should avoid this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight. To report suspected adverse drug events, for technical assistance or to obtain a copy of the SDS, contact Cronus Pharma LLC at 1-844-227-6687 or 1-844-2-CRONUS. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

PRECAUTIONS: The effects of enrofloxacin on cattle or swine reproductive performance, pregnancy and lactation have not been adequately determined.

The long-term effects on articular joint cartilage have not been determined in pigs above market weight.

Subcutaneous injection in cattle and swine, or intramuscular injection in swine, can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

EnroPro™ 100 contains different excipients than other enrofloxacin products. The safety and efficacy of this formulation in species other than cattle and swine have not been determined.

Quinolone-class drugs should be used with caution in animals with known or suspected Central Nervous System (CNS) disorders. In such animals, quinolones have, in rare instances, been associated with CNS stimulation which may lead to convulsive seizures. Quinolone-class drugs have been shown to produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. See Animal Safety section for additional information.

ADVERSE REACTIONS: No adverse reactions were observed during clinical trials.

To report suspected adverse drug events, contact Cronus Pharma LLC at 1-844-227-6687. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or *http://www.fda.gov/reportanimalae*.

MICROBIOLOGY: Enrofloxacin is bactericidal and exerts its antibacterial effect by inhibiting bacterial DNA gyrase (a type II topoisomerase) thereby preventing DNA supercoiling and replication which leads to cell death.[1] Enrofloxacin is active against Gram-negative and Gram-positive bacteria.

EFFECTIVENESS:

Cattle: A total of 845 calves with naturally-occurring BRD were treated with enrofloxacin in eight field trials located in five cattle-feeding states. Response to treatment was compared to non-treated controls. Singledose and multiple-day therapy regimens were evaluated. BRD and mortality were significantly reduced in enrofloxacin-treated calves. No adverse reactions were reported in treated animals.

The effectiveness of enrofloxacin for the control of respiratory disease in cattle at high risk of developing BRD was evaluated in a six-location study in the U.S. and Canada. A total of 1,150 crossbred beef calves at high risk of developing BRD were enrolled in the study. Enrofloxacin (7.5 mg/kg BW) or an equivalent volume of sterile saline was administered as a single subcutaneous injection within two days after arrival. Cattle were observed daily for clinical signs of BRD and were evaluated for success on Day 14 posttreatment. Treatment success in the enrofloxacin group (497/573, 87.83%) was significantly higher (P = 0.0013) than success in the saline control group (455/571, 80.92%). In addition, there were more treatment successes (n = 13) than failures (n = 3) in the group of animals positive for M. bovis on Day 0 that were treated with enrofloxacin. No product-related adverse reactions were reported.

Swine: A total of 590 pigs were treated with enrofloxacin or saline in two separate natural infection SRD field trials. For the treatment of SRD, the success rate of enrofloxacin-treated pigs that were defined as "sick and febrile" (increased respiratory rate, labored or dyspneic breathing, depressed attitude and a rectal temperature ≥ 104°F) was statistically significantly greater than the success rate of saline-treated "sick and febrile" pigs. For the control of SRD, mean rectal temperature, mortality (one trial) and morbidity were statistically significantly lower for enrofloxacin-treated pigs in pens containing a percentage of "sick and febrile" pigs compared to saline-treated pigs.

The effectiveness of enrofloxacin administered as a single SC dose of 7.5 mg/kg BW for the treatment and control of SRD associated with *M. hyopneumoniae* was demonstrated using an induced infection model study and three single-site natural infection field studies. In the model study, 72 healthy pigs were challenged with a representative *M. hyopneumoniae* isolate and treated with enrofloxacin or saline. A statistically significant (P < 0.0001) decrease in the mean total lung lesion score was observed in the enrofloxacin-treated group (4%) compared with the saline-treated group (27%) at 10 days post-treatment. In two field studies evaluating effectiveness for treatment of SRD, a total of 300 pigs with clinical signs of SRD (moderate depression, moderately increased respiratory rate, and a rectal temperature of ≥ 104°F) were enrolled and treated with enrofloxacin or saline. At 7 days post-treatment, the cure rate was statistically significantly higher at each site (P < 0.0001) in the enrofloxacin-treated groups (61.3% and 92%) compared with the saline-treated groups (26.7% and 33.3%). In one field study evaluating effectiveness for control of SRD, a group of 400 pigs in which > 15% had clinical signs of SRD (moderate depression score, moderately increased respiratory rate, and a rectal temperature of ≥ 104°F) was enrolled and treated with enrofloxacin or saline. At 7 days post-treatment, the cure rate was statistically significantly higher (P < 0.0002) in the enrofloxacin-treated group (70.0%) compared with the saline-treated group (48.5%). In addition to *M. hyopneumoniae* , *B. bronchiseptica* was also isolated in sufficient numbers from these field studies to be included in the SRD treatment and control indications.

The effectiveness of enrofloxacin for the control of colibacillosis associated with E. coli was evaluated in a multi-site natural infection field study. At each site, when at least 5% of the pigs were defined as "clinically affected" (presence of diarrhea and either depression or gauntness), all pigs were administered enrofloxacin as a single IM dose of 7.5 mg/kg BW or an equivalent dose volume of saline. At 7 days posttreatment, the success rate was statistically significantly higher (P = 0.0350) in the enrofloxacin-treated group (61.5%) compared with the saline-treated group (44.7%).

The effectiveness of enrofloxacin administered as a single IM dose of 7.5 mg/kg BW for the treatment and control of SRD or as a single SC dose of 7.5 mg/kg BW for the control of colibacillosis was confirmed by demonstrating comparable serum enrofloxacin concentrations following IM or SC injection into the neck of healthy male and female pigs.

TOXICOLOGY: The oral LD50 for laboratory rats was greater than 5000 mg/kg of body weight. Ninety-day feeding studies in dogs and rats revealed no observable adverse effects at treatment rates of 3 and 40 mg/kg respectively. Chronic studies in rats and mice revealed no observable adverse effects at 5.3 and 323 mg/kg respectively. There was no evidence of carcinogenic effect in laboratory animal models. A two-generation rat reproduction study revealed no effect with 10 mg/kg treatments. No teratogenic effects were observed in rabbits at doses of 25 mg/kg or in rats at 50 mg/kg.

ANIMAL SAFETY:
Cattle: Safety studies were conducted in feeder calves using single doses of 5, 15 and 25 mg/kg for 15 consecutive days and 50 mg/kg for 5 consecutive days. No clinical signs of toxicity were observed when a dose of 5 mg/kg was administered for 15 days. Clinical signs of depression, incoordination and muscle fasciculation were observed in calves when doses of 15 or 25 mg/kg were administered for 10 to 15 days. Clinical signs of depression, inappetance and incoordination were observed when a dose of 50 mg/kg was administered for 3 days. No drug-related abnormalities in clinical pathology parameters were identified. No articular cartilage lesions were observed after examination of stifle joints from animals administered 25 mg/kg for 15 days.

A safety study was conducted in 23-day-old calves using doses of 5, 15 and 25 mg/kg for 15 consecutive days. No clinical signs of toxicity or changes in clinical pathology parameters were observed. No articular cartilage lesions were observed in the stifle joints at any dose level at 2 days and 9 days following 15 days of drug administration.

An injection site study conducted in feeder calves demonstrated that the formulation may induce a transient reaction in the subcutaneous tissue and underlying muscle. No painful responses to administration were observed.

Swine: Subcutaneous Safety: A safety study was conducted in 32 pigs weighing approximately 57 kg (125 lb) using single doses of 5, 15, or 25 mg/kg daily for 15 consecutive days. Incidental lameness of short duration was observed in all groups, including the saline-treated controls. Musculoskeletal stiffness was observed following the 15 and 25 mg/kg treatments with clinical signs appearing during the second week of treatment. Clinical signs of lameness improved after treatment ceased and most animals were clinically normal at necropsy.

A second study was conducted in two pigs weighing approximately 23 kg (50 lb), treated with 50 mg/kg for 5 consecutive days. There were no clinical signs of toxicity or pathological changes.

An injection site study conducted in pigs demonstrated that the formulation may induce a transient reaction in the subcutaneous tissue. No painful responses to administration were observed.

Intramuscular Safety: A safety study was conducted in 48 weaned, 20- to 22-day-old pigs. Pigs were administered enrofloxacin, at 7.5, 22.5 and 37.5 mg/kg BW by IM injection into the neck once weekly for 3 consecutive weeks. All pigs remained clinically normal throughout the study. Transient decreases in feed and water consumption were observed after each treatment. Mild, transient, post-treatment injection site swellings were observed in pigs receiving the 37.5 mg/kg BW dose. Injection site inflammation was found on post-mortem examination in all enrofloxacin-treated groups.

STORAGE CONDITIONS: Protect from direct sunlight. Do not refrigerate or freeze. Store at 20°C to 25°C (68°F to 77°F), with an excursion permitted between 15°C and 30°C (between 59°F and 86°F). Precipitation may occur due to cold temperature. To re-dissolve, warm and then shake the vial.

HOW SUPPLIED:
EnroPro™ 100:
100 mg/mL-100 mL Bottle
100 mg/mL-250 mL Bottle
100 mg/mL-500 mL Bottle

REFERENCES:

1. Hooper, D.C., Wolfson, J.S., Quinolone Antimicrobial Agents, 2nd ed, 59 - 75, 1993

Approved by FDA under ANADA # 200-765

TAKE TIME. OBSERVE LABEL DIRECTIONS.

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816
Contact No: 1-844-227-6687
(1-844-2-CRONUS)

Code: 4206162/TS/DRUGS/2023
Made in India
Revised: 08/2024
PC048-00

FLORFENIJECT™ (FLORFENICOL) INJECTABLE SOLUTION (300 mg/mL)

For intramuscular and subcutaneous use in beef and non-lactating dairy cattle only
Not for use in female dairy cattle 20 months of age or older or in calves to be processed for veal.

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: FLORFENIJECT Injectable Solution is a solution of the synthetic antibiotic florfenicol. Each milliliter of sterile FLORFENIJECT Injectable Solution contains 300 mg of florfenicol, 250 mg *N*-methyl-2-pyrrolidone (NMP), 150 mg propylene glycol, and polyethylene glycol qs. The chemical name for florfenicol is *2,2-Dichloro-N-[1-(fluoromethyl)-2-hydroxy-2-[4-(methylsulfonyl)phenyl]ethyl] acetamide.*

INDICATIONS: FLORFENIJECT Injectable Solution is indicated for treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni,* and for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*. Also, it is indicated for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni.*

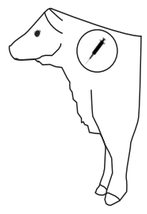
DOSAGE AND ADMINISTRATION: For treatment of bovine respiratory disease (BRD) and bovine interdigital phlegmon (foot rot): FLORFENIJECT Injectable Solution should be administered by intramuscular injection to cattle at a dose rate of 20 mg/kg body weight (3 mL/100 lbs). A second dose should be administered 48 hours later. Alternatively, FLORFENIJECT Injectable Solution can be administered by a single subcutaneous (SC) injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100 lbs). Do not administer more than 10 mL at each site. The injection should be given only in the neck.

NOTE: Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.

For control of respiratory disease in cattle at high-risk of developing BRD: FLORFENIJECT Injectable Solution should be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100 lbs). Do not administer more than 10 mL at each site. The injection should be given only in the neck.

FLORFENIJECT Injectable Solution DOSAGE GUIDE		
ANIMAL WEIGHT (lbs)	IM FLORFENIJECT DOSAGE 3.0 mL/100 lb Body Weight (mL)	SC FLORFENIJECT DOSAGE 6.0 mL/100 lb Body Weight (mL)
100	3.0	6.0
200	6.0	12.0
300	9.0	18.0
400	12.0	24.0
500	15.0	30.0
600	18.0	36.0
700	21.0	42.0
800	24.0	48.0
900	27.0	54.0
1000	30.0	60.0

Recommended Injection Location



Do not inject more than 10 mL per injection site.

Clinical improvement should be evident in most treated subjects within 24 hours of initiation of treatment. If a positive response is not noted within 72 hours of initiation of treatment, the diagnosis should be re-evaluated.

CONTRAINDICATIONS: Do not use in animals that have shown hypersensitivity to florfenicol.

WARNINGS:
User Safety Warnings:
Not for use in humans. Keep out of reach of children.

This product contains materials that can be irritating to skin and eyes. Avoid direct contact with skin, eyes, and clothing. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. Consult a physician if irritation persists. Accidental injection of this product may cause local irritation. Consult a physician immediately.

Reproductive and developmental toxicities have been reported in laboratory animals following high, repeated exposures to *N*-methyl-2-pyrrolidone (NMP). Pregnant women should wear gloves and exercise caution or avoid handling this product.

The Safety Data Sheet (SDS) contains more detailed occupational safety information.

CONTACT INFORMATION: To report suspected adverse drug events, for technical assistance or to obtain a copy of the SDS, contact Cronus Pharma LLC at 1-844-227-6687. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

PRECAUTIONS: Not for use in animals intended for breeding purposes. The effects of florfenicol on bovine reproductive performance, pregnancy, and lactation have not been determined. Toxicity studies in dogs, rats, and mice have associated the use of florfenicol with testicular degeneration and atrophy. Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.

RESIDUE WARNINGS: Animals intended for human consumption must not be slaughtered within 28 days of the last intramuscular treatment. Animals intended for human consumption must not be slaughtered within 38 days of subcutaneous treatment. This product is not approved for use in female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or in calves born to these cows. A withdrawal period has not been established in pre-ruminating calves. Do not use in calves to be processed for veal.

ADVERSE REACTIONS: Inappetence, decreased water consumption, or diarrhea may occur transiently following treatment.

CLINICAL PHARMACOLOGY: The pharmacokinetic disposition of Florfenicol Injectable Solution was evaluated in feeder calves following single intramuscular (IM) administration at the recommended dose of 20 mg/kg body weight. Florfenicol Injectable Solution was also administered intravenously (IV) to the same cattle in order to calculate the volume of distribution, clearance, and percent bioavailability1 (Table 1).

TABLE 1. Pharmacokinetic Parameter Values for Florfenicol Following IM Administration of 20 mg/kg Body Weight to Feeder Calves (n=10).

Parameter	Median	Range
C_{max} (µg/mL)	3.07*	1.43-5.60
t_{max} (hr)	3.33	0.75-8.00
T ½ (hr)	18.3†	8.30 - 44.0
AUC (µg•min/mL)	4242	3200 - 6250
Bioavailability (%)	78.5	59.3 - 106
Vd_{ss} (L/kg)‡	0.77	0.68 - 0.85
Cl_t (mL/min/kg)‡	3.75	3.17 - 4.31

C_{max} Maximum serum concentration
T_{max} Time at which C_{max} is observed
T ½ Biological half-life
AUC Area under the curve
Vd_{ss} Volume of distribution at steady state
Cl_t Total body clearance
*harmonic mean
†mean value
‡following IV administration

Florfenicol was detectable in the serum of most animals through 60 hours after intramuscular administration with a mean concentration of 0.19 µg/mL. The protein binding of florfenicol was 12.7%, 13.2%, and 18.3% at serum concentrations of 0.5, 3.0, and 16.0 µg/mL, respectively.

MICROBIOLOGY: Florfenicol is a synthetic, broad-spectrum antibiotic active against many Gram negative and Gram-positive bacteria isolated from domestic animals. It acts by binding to the 50S ribosomal subunit and inhibiting bacterial protein synthesis. Florfenicol is generally considered a bacteriostatic drug, but exhibits bactericidal activity against certain bacterial species. *In vitro* studies demonstrate that florfenicol is active against the bovine respiratory disease (BRD) pathogens *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni,* and that florfenicol exhibits bactericidal activity against strains of *M. haemolytica and H. somni.* Clinical studies confirm the efficacy of florfenicol against BRD as well as against commonly isolated bacterial pathogens in bovine interdigital phlegmon including *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.

The minimum inhibitory concentrations (MICs) of florfenicol for BRD organisms were determined using isolates obtained from natural infections from 1990 to 1993. The MICs for interdigital phlegmon organisms were determined using isolates obtained from natural infections from 1973 to 1997 (Table 2).

TABLE 2. Florfenicol Minimum Inhibitory Concentration (MIC) Values* of Indicated Pathogens Isolated From Natural Infections of Cattle.

Indicated pathogens	Year of isolation	Isolate Numbers	MIC_{50} † (µg/mL)	MIC_{90} † (µg/mL)
Mannheimia haemolytica	1990 to 1993	398	0.5	1
Pasteurella multocida	1990 to 1993	350	0.5	0.5
Histophilis somni	1990 to 1993	66	0.25	0.5
Fusobacterium necrophorum	1973 to 1997	33	0.25	0.25
Bacteroides melaninogenicus	1973 to 1997	20	0.25	0.25

*The correlation between the *in vitro* susceptibility data and clinical effectiveness is unknown.
† The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

ANIMAL SAFETY: A 10x safety study was conducted in feeder calves. Two intramuscular injections of 200 mg/kg were administered at a 48-hour interval. The calves were monitored for 14 days after the second dose. Marked anorexia, decreased water consumption, decreased body weight, and increased serum enzymes were observed following dose administration. These effects resolved by the end of the study.

A 1x, 3x, and 5x (20, 60, and 100 mg/kg) safety study was conducted in feeder calves for 3x the duration of treatment (6 injections at 48-hour intervals). Slight decrease in feed and water consumption was observed in the 1x dose group. Decreased feed and water consumption, body weight, urine pH, and increased serum enzymes, were observed in the 3x and 5x dose groups. Depression, soft stool consistency, and dehydration were also observed in some animals (most frequently at the 3x and 5x dose levels), primarily near the end of dosing.

A 43-day controlled study was conducted in healthy cattle to evaluate effects of florfenicol injectable solution administered at the recommended dose on feed consumption. Although a transient decrease in feed consumption was observed, Florfenicol Injectable Solution administration had no long-term effect on body weight, rate of gain, or feed consumption.

STORAGE INFORMATION: Store at 20°C to 25°C (68°F to 77°F), with an excursion permitted between 15°C and 30°C (between 59°F and 86°F).

Protect from light when not in use.

Use within 30 days of first puncture. For the 100mL vials, puncture the stopper a maximum of 3 times. For the 250mL and 500mL vials, puncture the stopper a maximum of 17 times. If more than the specified punctures are anticipated, the use of multi-dosing equipment is recommended. When using a draw-off spike or needle with bore diameter larger than 16-gauge, discard any product remaining in the vial immediately after use.

HOW SUPPLIED: FLORFENIJECT Injectable Solution is packaged in 100 mL (NDC 69043-044-10), 250 mL (NDC 69043-044-25), and 500 mL (NDC 69043-044-50) glass sterile multiple-dose vials.

REFERENCE: 1. Lobell RD, Varma KJ, et al. Pharmacokinetics of florfenicol following intravenous and intramuscular doses to cattle. J Vet Pharmacol Therap. 1994;17:253-258.

Florfeniject™ is the trademark of Cronus Pharma LLC

Approved by FDA under ANADA # 200-760

TAKE TIME. OBSERVE LABEL DIRECTIONS.

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816
Contact No: 1-844-227-6687
(1-844-2-CRONUS)

Code: 4206162/TS/DRUGS/2023
Made in India
Revised: 01/2024
PC044-00

SULFADIMETHOXINE CONCENTRATED SOLUTION 12.5%

INDICATIONS
BROILER AND REPLACEMENT CHICKENS: Use for the treatment of disease outbreaks of coccidiosis, fowl cholera, and infectious coryza.
MEAT PRODUCING TURKEYS: Use for the treatment of disease outbreaks of coccidiosis and fowl cholera.
DAIRY CALVES, DAIRY HEIFERS AND BEEF CATTLE: Use for the treatment of shipping fever complex and bacterial pneumonia associated with *Pasteurella* spp. sensitive to sulfadimethoxine, calf diphtheria and foot rot associated with *Fusobacterium necrophorum (Sphaerophorus necrophorus)* sensitive to sulfadimethoxine.

PRECAUTIONS
Store at controlled room temperature 20° to 25°C (68° to 77°F), excursions permitted from 15° to 30°C (59° to 86°F). If freezing occurs, thaw before using. Protect from light; direct sunlight may cause discoloration. Freezing or discoloration does not affect potency. Prepare a fresh stock solution daily.
CHICKENS AND TURKEYS: If animals show no improvement within 5 days, discontinue treatment and re-evaluate diagnosis. Handle the recommended dilutions (chickens 0.05% and turkeys 0.025%) as regular drinking water. Administer as sole source of drinking water and sulfonamide medication.
Chickens and turkeys that have survived fowl cholera outbreaks should not be kept for replacements or breeders.
CATTLE: During treatment period, make certain that animals maintain adequate water intake. If animals show no improvement within 2 or 3 days, re-evaluate diagnosis. Treatment should not be continued beyond 5 days.
FOR USE IN ANIMALS ONLY
NOT FOR USE IN HUMANS
KEEP OUT OF REACH OF CHILDREN

TAKE TIME OBSERVE LABEL DIRECTIONS

RESIDUE WARNINGS
Chickens and Turkeys – Withdraw 5 days before slaughter. Do not administer to chickens over 16 weeks (112 days) of age or to turkeys over 24 weeks (168 days) of age.
Cattle – Withdraw 7 days before slaughter. For dairy calves, dairy heifers and beef cattle only.
A withdrawal period has not been established for this product in pre-ruminating calves.
Do Not Use in Calves to be Processed for Veal
Restricted Drug (California) – Use Only as Directed

DO NOT SLAUGHTER COW FOR
7 DAYS
AFTER LAST TREATMENT

3 69043 02589 1

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816
Contact No.: 1-844-227-6687
(1-844-2-CRONUS)

S-2766-07
Rev. 04-20

Lot No.: Exp. Date:

NDC 69043-025-89

Sulfadimethoxine
Concentrated Solution 12.5%

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

ANTIBACTERIAL
for Use in Drinking Water

For Oral Use in Chickens, Turkeys, and Cattle

Approved by FDA under ANADA # 200-165

NET CONTENTS: 1 GALLON (3.785 liters)

PROTECT FROM LIGHT

Cronus Pharma

3.75 g sulfadimethoxine/fl oz.
Dosage and Administration

Chickens and Turkeys

Treatment Period: 6 consecutive days
Recommended Concentrations: Chickens – 0.05%; Turkeys – 0.025%
Chickens Add 1 fl oz (30 mL) to 2 gallons of drinking water -or- 25 fl oz to 50 gallons of drinking water.
Turkeys Add 1 fl oz (30 mL) to 4 gallons of drinking water -or- 25 fl oz to 100 gallons of drinking water.
Automatic Proportioners* Stock Solution – To make 2 gallons of Stock Solution use:
Chickens Add 1 gallon of Sulfadimethoxine Concentrated Solution 12.5% to 1 gallon of water
Turkeys Add 2 qts of Sulfadimethoxine Concentrated Solution 12.5% to 6 qts of water

*Set proportioner to a feed rate of 1 fl oz (30 mL) of Sulfadimethoxine Stock Solution per gallon of water.

Dairy Calves, Dairy Heifers, and Beef Cattle

Treatment Period: 5 consecutive days
Dosage: Initial dose of 25 mg/lb followed by four maintenance doses of 12.5 mg/lb/day

Summer Administration
Dosage recommendations for summer are based on an estimated water intake of 1 gallon of water per every 100 lb of body weight per day.

Daily Drinking Water Supply	Sulfadimethoxine Concentrated Solution 12.5% Initial Dose	Maintenance Dose
25 gal	1 pt (16 fl oz)	1 cup (8 fl oz)
50 gal	1 qt (32 fl oz)	1 pt (16 fl oz)
200 gal	1 gal (128 fl oz)	2 qt (64 fl oz)

Winter Administration
Dosage recommendations for winter are based on an estimated water intake of 1 gallon of water per every 150 lb of body weight per day.

Daily Drinking Water Supply	Sulfadimethoxine Concentrated Solution 12.5% Initial Dose	Maintenance Dose
16 gal	1 pt (16 fl oz)	1 cup (8 fl oz)
33 gal	1 qt (32 fl oz)	1 pt (16 fl oz)
127 gal	1 gal (128 fl oz)	2 qt (64 fl oz)

For individual treatment of cattle, Sulfadimethoxine Concentrated Solution 12.5% may be given as a drench. Administer using an initial dose of 25 mg/lb followed by 4 maintenance doses of 12.5 mg/lb/day. One fl oz will medicate one 150-lb animal initially and 1/2 fl oz will medicate one 150-lb animal on maintenance dose.

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816
Contact No: 1-844-227-6687
(1-844-2-CRONUS)

Revised: 04/20

TAKE TIME. OBSERVE LABEL DIRECTIONS.

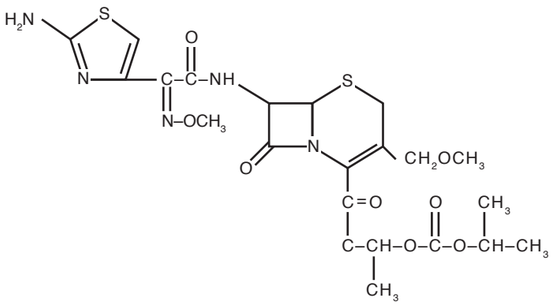
CEFPODOXIME PROXETIL TABLETS

cefpodoxime proxetil tablet, film coated
Cefpodoxime Proxetil Tablets , USP

Rx only: To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefpodoxime proxetil and other antibacterial drugs, cefpodoxime proxetil should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

For Oral Use Only

DESCRIPTION: Cefpodoxime proxetil is an orally administered, extended spectrum, semi-synthetic antibiotic of the cephalosporin class. The chemical name is (RS)-1(isopropoxycarbonyloxy) ethyl (+)-(6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-{(Z)methoxyimino} acetamido}-3-methoxymethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene- 2-carboxylate. Its molecular formula is C H N O S and its structural formula is represented below:



The molecular weight of cefpodoxime proxetil is 557.6.

Cefpodoxime proxetil is a prodrug; its active metabolite is cefpodoxime. All doses of cefpodoxime proxetil in this insert are expressed in terms of the active cefpodoxime moiety. The drug is supplied as film-coated tablets.

Cefpodoxime proxetil tablets, USP contain cefpodoxime proxetil USP equivalent to 100 mg or 200 mg of cefpodoxime activity and the following inactive ingredients: carboxy methyl cellulose calcium, lactose monohydrate, hydroxy propyl cellulose, sodium lauryl sulfate, crospovidone, corn starch, magnesium stearate, hypromellose, titanium dioxide, propylene glycol and FD&C yellow #6 aluminum lake. In addition, the 100 mg film-coated tablets contain iron oxide yellow and the 200 mg film-coated tablets contain FD&C red #40 aluminum lake.

CLINICAL PHARMACOLOGY
Absorption and Excretion: Cefpodoxime proxetil is a prodrug that is absorbed from the gastrointestinal tract and de-esterified to its active metabolite, cefpodoxime. Following oral administration of 100 mg of cefpodoxime proxetil to fasting subjects, approximately 50% of the administered cefpodoxime dose was absorbed systemically. Over the recommended dosing range (100 to 400 mg), approximately 29 to 33% of the administered cefpodoxime dose was excreted unchanged in the urine in 12 hours. There is minimal metabolism of cefpodoxime in vivo.

Effects of Food: The extent of absorption (mean AUC) and the mean peak plasma concentration increased when filmcoated tablets were administered with food. Following a 200 mg tablet dose taken with food, the AUC was 21 to 33% higher than under fasting conditions, and the peak plasma concentration averaged 3.1 mcg/mL in fed subjects versus 2.6 mcg/mL in fasted subjects. Time to peak concentration was not significantly different between fed and fasted subjects. When a 200 mg dose of the suspension was taken with food, the extent of absorption (mean AUC) and mean peak plasma concentration in fed subjects were not significantly different from fasted subjects, but the rate of absorption was slower with food (48% increase in T_{max}).

Pharmacokinetics of Cefpodoxime Proxetil Film-coated Tablets: Over the recommended dosing range (100 to 400 mg), the rate and extent of cefpodoxime absorption exhibited dose-dependency; dose-normalized C_{max} and AUC decreased by up to 32% with increasing dose. Over the recommended dosing range, the T_{max} was approximately 2 to 3 hours and the $T_{1/2}$ ranged from 2.09 to 2.84 hours. Mean C_{max} was 1.4 mcg/mL for the 100 mg dose, 2.3 mcg/mL for the 200 mg dose, and 3.9 mcg/mL for the 400 mg dose. In patients with normal renal function, neither accumulation nor significant changes in other pharmacokinetic parameters were noted following multiple oral doses of up to 400 mg Q 12 hours.

CEFPODOXIME PLASMA LEVELS (mcg/mL) IN FASTED ADULTS AFTER FILMCOATED TABLET ADMINISTRATION (Single Dose)

Dose (cefpodoxime equivalents)	Time after oral ingestion						
	1HR	2HR	3HR	4HR	6HR	8HR	12HR
100mg	0.98	1.4	1.3	1	0.59	0.29	0.08
200mg	1.5	2.2	2.2	1.8	1.2	0.62	0.18
400mg	2.2	3.7	3.8	3.3	2.3	1.3	0.38

Pharmacokinetics of Cefpodoxime Proxetil Suspension:
In adult subjects, a 100 mg dose of oral suspension produced an average peak cefpodoxime concentration of approximately 1.5 mcg/mL (range: 1.1 to 2.1 mcg/mL), which is equivalent to that reported following administration of the 100 mg tablet. Time to peak plasma concentration and area under the plasma concentration-time curve (AUC) for the oral suspension were also equivalent to those produced with film-coated tablets in adults following a 100 mg oral dose. The pharmacokinetics of cefpodoxime were investigated in 29 patients aged 1 to 17 years. Each patient received a single, oral, 5 mg/kg dose of cefpodoxime oral suspension. Plasma and urine samples were collected for 12 hours after dosing. The plasma levels reported from this study are as follows:

CEFPODOXIME PLASMA LEVELS (mcg/mL) IN FASTED PATIENTS (1 to 17 YEARS OF AGE) AFTER SUSPENSION ADMINISTRATION

Dose (cefpodoxime equivalents)	Time after oral ingestion						
	1HR	2HR	3HR	4HR	6HR	8HR	12HR
5 mg/kg[1]	1.4	2.1	2.1	1.7	0.9	0.4	0.09

[1]Dose did not exceed 200 mg.

DISTRIBUTION
Protein binding of cefpodoxime ranges from 22 to 33% in serum and from 21 to 29% in plasma.

Skin Blister: Following multiple-dose administration every 12 hours for 5 days of 200 mg or 400 mg cefpodoxime proxetil, the mean maximum cefpodoxime concentration in skin blister fluid averaged 1.6 and 2.8 mcg/mL, respectively. Skin blister fluid cefpodoxime levels at 12 hours after dosing averaged 0.2 and 0.4 mcg/mL for the 200 mg and 400 mg multiple-dose regimens, respectively.

Tonsil Tissue: Following a single, oral 100 mg cefpodoxime proxetil film-coated tablet, the mean maximum cefpodoxime concentration in tonsil tissue averaged 0.24 mcg/g at 4 hours post-dosing and 0.09 mcg/g at 7 hours post-dosing. Equilibrium was achieved between plasma and tonsil tissue within 4 hours of dosing. No detection of cefpodoxime in tonsillar tissue was reported 12 hours after dosing. These results demonstrated that concentrations of cefpodoxime exceeded the MIC of S. pyogenes for at least 7 hours after dosing of 100 mg of cefpodoxime proxetil.

Lung Tissue: Following a single, oral 200 mg cefpodoxime proxetil film-coated tablet, the mean maximum cefpodoxime concentration in lung tissue averaged 0.63 mcg/g at 3 hours post-dosing, 0.52 mcg/g at 6 hours post-dosing, and 0.19 mcg/g at 12 hours post-dosing. The results of this study indicated that cefpodoxime penetrated into lung tissue and produced sustained drug concentrations for at least 12 hours after dosing at levels that exceeded the MIC for S. pneumoniae and H. influenzae.

CSF: Adequate data on CSF levels of cefpodoxime are not available.

Effects of Decreased Renal Function: Elimination of cefpodoxime is reduced in patients with moderate to severe renal impairment (<50 mL/min creatinine clearance). (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.) In subjects with mild impairment of renal function (50 to 80 mL/min creatinine clearance), the average plasma half-life of cefpodoxime was 3.5 hours. In subjects with moderate (30 to 49 mL/min creatinine clearance) or severe renal impairment (5 to 29 mL/min creatinine clearance), the half-life increased to 5.9 and 9.8 hours, respectively. Approximately 23% of the administered dose was cleared from the body during a standard 3-hour hemodialysis procedure.

Effect of Hepatic Impairment (cirrhosis): Absorption was somewhat diminished and elimination unchanged in patients with cirrhosis. The mean cefpodoxime T and renal clearance in cirrhotic patients were similar to those derived in studies of healthy subjects. Ascites did not appear to affect values in cirrhotic subjects. No dosage adjustment is recommended in this patient population.

Pharmacokinetics in Elderly Subjects:
Elderly subjects do not require dosage adjustments unless they have diminished renal function. (See PRECAUTIONS.) In healthy geriatric subjects, cefpodoxime half-life in plasma averaged 4.2 hours (vs 3.3 in younger subjects) and urinary recovery averaged 21% after a 400 mg dose was administered every 12 hours. Other pharmacokinetic parameters (C_{max}, AUC, and T_{max}) were unchanged relative to those observed in healthy young subjects.

MICROBIOLOGY
Mechanism of Action: Cefpodoxime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Cefpodoxime has activity in the presence of some beta-lactamases, both penicillinases and cephalosporinases, of Gram-negative and Gram-positive bacteria.

Mechanism of Resistance: Resistance to cefpodoxime is primarily through hydrolysis by beta-lactamase, alteration of penicillinbinding proteins (PBPs), and decreased permeability. Cefpodoxime has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections as described in the Indications and Usage (1) section:

Gram-positive bacteria:
Staphylococcus aureus (methicillin-susceptible strains, including those producing penicillinases)
Staphylococcus saprophyticus
Streptococcus pneumoniae (excluding penicillin-resistant isolates)
Streptococcus pyogenes

Gram-negative bacteria:
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Haemophilus influenzae (including beta-lactamase producing isolates)
Moraxella catarrhalis
Neisseria gonorrhoeae (including penicillinase-producing isolates)

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for cefpodoxime. However, the efficacy of cefpodoxime in treating clinical infections due to these microorganisms has not been established in adequate and wellcontrolled clinical trials.

Gram-positive bacteria:
Streptococcus agalactiae
Streptococcus spp. (Groups C, F, G)

Gram-negative bacteria:
Citrobacter diversus
Klebsiella oxytoca
Proteus vulgaris
Providencia rettgeri
Haemophilus parainfluenzae
max max

Anaerobic Gram-pos itive bacteria:
Peptostreptococcus magnus

Susceptibility Testing
For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

INDICATIONS AND USAGE
Cefpodoxime proxetil is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Recommended dosages, durations of therapy, and applicable patient populations vary among thes e infections. Please see DOSAGE AND ADMINISTRATION for specific recommendations. Acute otitis media caused by *Streptococcus pneumoniae* (excluding penicillin-resistant strains), *Streptococcus pyogenes, Haemophilus influenzae* (including beta-lactamase-producing strains), or *Moraxella (Branhamella) catarrhalis* (including beta-lactamase-producing strains).

Pharyngitis and/or tonsillitis caused by Streptococcus pyogenes.

NOTE: Only penicillin by the intramuscular route of administration has been shown to be effective in the prophylaxis of rheumatic fever. Cefpodoxime proxetilis generally effective in the eradication of streptococci from the oropharynx. However, data establishing the efficacy of cefpodoxime proxetil for the prophylaxis of subsequent rheumatic fever are not available.

Community-acquired pneumonia caused by *S. pneumoniae* or *H. Influenzae* (including betalactamase-producing strains).

Acute bacterial exacerbation of chronic bronchitis caused by *S. pneumoniae, H. influenzae* (non-betalactamase-producing strains only), or *M. catarrhalis*. Data are insufficient at this time to establish efficacy in patients with acute bacterial exacerbations of chronic bronchitis caused by beta-lactamaseproducing strains of *H. influenzae.*

Acute, uncomplicated urethral and cervical gonorrhea caused by *Neisseria gonorrhoeae* (including penicillinase-producing strains).

Acute, uncomplicated ano-rectal infections in women due to *Neisseria gonorrhoeae* (including penicillinase-producing strains).

NOTE: The efficacy of cefpodoxime in treating male patients with rectal infections caused by *N. gonorrhoeae* has not been established. Data do not support the use of cefpodoxime proxetil in the treatment of pharyngeal infections due to *N. gonorrhoeae* in men or women.

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (including penicillinase-producing strains) or *Streptococcus pyogenes*. Abscesses should be surgically drained as clinically indicated.

NOTE: In clinical trials, successful treatment of uncomplicated skin and skin structure infections was dose-related. The effective therapeutic dose for skin infections was higher than those used in other recommended indications. (See **DOSAGE AND ADMINISTRATION.**)

Acute maxillary s inusitis caused by *Haemophilus influenzae* (including beta-lactamase-producing strains), *Streptococcus pneumoniae*, and *Moraxella catarrhalis*.

Uncomplicated urinary tract infections (cystitis) caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* or *Staphylococcus saprophyticus.*

NOTE: In considering the use of cefpodoxime proxetil in the treatment of cystitis, cefpodoxime proxetil's lower bacterial eradication rates should be weighed against the increased eradication rates and different safety profiles of some other classes of approved agents. (See **CLINICAL STUDIES** section.)

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibility to cefpodoxime. Therapy may be instituted while awaiting the results of these studies. Once these results become available, antimicrobial therapy should be adjusted accordingly. To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefpodoxime proxetil and other antibacterial drugs, cefpodoxime proxetil should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS
Cefpodoxime proxetil is contraindicated in patients with a known allergy to cefpodoxime or to the cephalosporin group of antibiotics.

WARNINGS
BEFORE THERAPY WITH CEFPODOXIME PROXETIL IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFPODOXIME, OTHER CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF CEFPODOXIME IS TO BE ADMINISTERED TO PENICILLIN SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFPODOXIME PROXETIL OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINE, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including cefpodoxime proxetil, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

A concerted effort to monitor for *C. difficile* in cefpodoxime-treated patients with diarrhea was undertaken because of an increased incidence of diarrhea associated with *C. difficile* in early trials in normal subjects. *C. difficile* organisms or toxin was reported in 10% of the cefpodoxime-treated adult patients with diarrhea; however, no specific diagnosis of pseudomembranous colitis was made in these patients.

In post-marketing experience outside the United States, reports of pseudomembranous colitis associated with the use of cefpodoxime proxetil have been received.

PRECAUTIONS
General: In patients with transient or persistent reduction in urinary output due to renal insufficiency, the total daily dose of cefpodoxime proxetil should be reduced because high and prolonged serum antibiotic concentrations can occur in such individuals following usual doses. Cefpodoxime, like other cephalosporins, should be administered with caution to patients receiving concurrent treatment with potent diuretics. (See **DOSAGE AND ADMINISTRATION.**)

As with other antibiotics, prolonged use of cefpodoxime proxetil may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Prescribing cefpodoxime proxetil in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients : Patients should be counseled that antibacterial drugs including cefpodoxime proxetil should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When cefpodoxime proxetil is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by cefpodoxime proxetil or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

DRUG INTERACTIONS
Antacids: Concomitant administration of high doses of antacids (sodium bicarbonate and aluminum hydroxide) or H blockers reduces peak plasma levels by 24% to 42% and the extent of absorption by 27% to 32%, respectively. The rate of absorption is not altered by these concomitant medications. Oral anti-cholinergics (e.g., propantheline) delay peak plasma levels (47% increase in T_{max}), but do not affect the extent of absorption (AUC).

Probenecid: As with other beta-lactam antibiotics, renal excretion of cefpodoxime was inhibited by probenecid and resulted in an approximately 31% increase in AUC and 20% increase in peak cefpodoxime plasma levels.

Nephrotoxic drugs: Although nephrotoxicity has not been noted when cefpodoxime proxetil was given alone, close monitoring of renal function is advised when cefpodoxime proxetil is administered concomitantly with compounds of known nephrotoxic potential.

DRUG/LABORATORY TEST INTERACTIONS
Cephalosporins, including cefpodoxime proxetil, are known to occasionally induce a positive direct Coombs' test.

Carcinogenesis , Mutagenesis , Impairment of Fertility: Long-term animal carcinogenesis studies of cefpodoxime proxetil have not been performed. Mutagenesis studies of cefpodoxime, including the Ames test both with and without metabolic activation, the chromosome aberration test, the unscheduled DNA synthesis assay, mitotic recombination and gene conversion, the forward gene mutation assay and the *in vivo* micronucleus test, were all negative. No untoward effects on fertility or reproduction were noted when 100 mg/kg/day or less (2 times the human dose based on mg/m²) was administered orally to rats.

PREGNANCY
Teratogenic Effects

Pregnancy Category B
Cefpodoxime proxetil was neither teratogenic nor embryocidal when administered to rats during organogenesis at doses up to 100 mg/kg/day (2 times the human dose based on mg/m²) or to rabbits at doses up to 30 mg/kg/day (1 to 2 times the human dose based on mg/m²).

There are, however, no adequate and well-controlled studies of cefpodoxime proxetil use in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Cefpodoxime proxetil has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers: Cefpodoxime is excreted in human milk. In a study of 3 lactating women, levels of cefpodoxime in human milk were 0%, 2% and 6% of concomitant serum levels at 4 hours following a 200 mg oral dose of cefpodoxime proxetil. At 6 hours post-dosing, levels were 0%, 9% and 16% of concomitant serum levels. Because of the potential for serious reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and efficacy in infants less than 2 months of age have not been established.

Geriatric Use: Of the 3338 patients in multiple-dose clinical studies of cefpodoxime proxetil film-coated tablets, 521 (16%) were 65 and over, while 214 (6%) were 75 and over. No overall differences in effectiveness or safety were observed between the elderly and younger patients. In healthy geriatric subjects with normal renal function, cefpodoxime half-life in plasma averaged 4.2 hours and urinary recovery averaged 21% after a 400 mg dose was given every 12 hours for 15 days. Other pharmacokinetic parameters were unchanged relative to those observed in healthy younger subjects.

Dose adjustment in elderly patients with normal renal function is not necessary.

ADVERSE REACTIONS

Clinical Trials :

Film-coated Tablets (Multiple dose):
In clinical trials using **multiple doses** of cefpodoxime proxetil film-coated tablets, 4696 patients were treated with the recommended dosages of cefpodoxime (100 to 400 mg Q 12 hours). There were no deaths or permanent disabilities thought related to drug toxicity. One-hundred twenty-nine (2.7%) patients discontinued medication due to adverse events thought possibly or probably related to drug toxicity. Ninety-three (52%) of the 178 patients who discontinued therapy (whether thought related to drug therapy or not) did so because of gastrointestinal disturbances, nausea, vomiting, or diarrhea. The percentage of cefpodoxime proxetil-treated patients who discontinued study drug because of adverse events was significantly greater at a dose of 800 mg daily than at a dose of 400 mg daily or at a dose of 200 mg daily. Adverse events thought possibly or probably related to cefpodoxime in multiple-dose clinical trials (N=4696 cefpodoxime-treated patients) were:

Incidence Greater Than 1%:

Diarrhea	7%

Diarrhea or loose stools were dose-related: decreasing from 10.4% of patients receiving 800 mg per day to 5.7% for those receiving 200 mg per day. Of patients with diarrhea, 10% had C. difficile organism or toxin in the stool. (See **WARNINGS.**)

Nausea	3.3%
Vaginal Fungal Infections	1%
Vulvovaginal Infections	1.3%
Abdominal Pain	1.2%
Headache	1%

Incidence Less Than 1%: By body system in decreasing order:

CLINICAL STUDIES

Adverse events thought possibly or probably related to cefpodoxime proxetil that occurred in les s than 1% of patients (N=4696)

Body - fungal infections, abdominal distention, malaise, fatigue, asthenia, fever, chest pain, back pain, chills, generalized pain, abnormal microbiological tests, moniliasis, abscess, allergic reaction, facial edema, bacterial infections, parasitic infections, localized edema, localized pain.

Cardiovascular - congestive heart failure, migraine, palpitations, vasodilation, hematoma, hypertension, hypotension.

Digestive - vomiting, dyspepsia, dry mouth, flatulence, decreased appetite, constipation, oral moniliasis, anorexia, eructation, gastritis, mouth ulcers, gastrointestinal disorders, rectal disorders, tongue disorders, tooth disorders, increased thirst, oral lesions, tenesmus, dry throat, toothache.

Hemic and Lymphatic - anemia.

Metabolic and Nutritional - dehydration, gout, peripheral edema, weight increase.

Musculo-skeletal - myalgia.

Nervous - dizziness, insomnia, somnolence, anxiety, shakiness, nervousness, cerebral infarction, change in dreams, impaired concentration, confusion, nightmares, paresthesia, vertigo.

Respiratory - asthma, cough, epistaxis, rhinitis, wheezing, bronchitis, dyspnea, pleural effusion, pneumonia, sinusitis.

Skin - urticaria, rash, pruritus non-application site, diaphoresis, maculopapular rash, fungal dermatitis, desquamation, dry skin non-application site, hair loss, vesiculobullous rash, sunburn.

Special Senses - taste alterations, eye irritation, taste loss, tinnitus.

Urogenital - hematuria, urinary tract infections, metrorrhagia, dysuria, urinary frequency, nocturia, penile infection, proteinuria, vaginal pain.

GRANULES FOR ORAL SUSPENSION (MULTIPLE DOSE)
In clinical trials using multiple doses of cefpodoxime proxetil granules for oral suspension, 2128 pediatric patients (93% of whom were less than 12 years of age) were treated with the recommended dosages of cefpodoxime (10 mg/kg/day Q 24 hours or divided Q 12 hours to a maximum equivalent adult dose). There were no deaths or permanent disabilities in any of the patients in these studies. Twenty-four patients (1.1%) discontinued medication due to adverse events thought possibly or probably related to study drug. Primarily, these discontinuations were for gastrointestinal disturbances, usually diarrhea, vomiting, or rashes.

Adverse events thought possibly or probably related, or of unknown relationship to cefpodoxime proxetil for oral suspension in multiple-dose clinical trials (N=2128 patients treated with cefpodoxime) were:

Incidence Greater Than 1%:

Diarrhea	6%

The incidence of diarrhea in infants and toddlers (age 1 month to 2 years) was 12.8%.

Diaper rash/Fungal skin rash	2% (includes moniliasis)

The incidence of diaper rash in infants and toddlers was 8.5%.

Other skin rashes	1.8%
Vomiting	2.3%

Incidence Less Than 1%:

Body: Localized abdominal pain, abdominal cramp, headache, monilia, generalized abdominal pain, asthenia, fever, fungal infection.

Digestive: Nausea, monilia, anorexia, dry mouth, stomatitis, pseudomembranous colitis.

Hemic & Lymphatic: Thrombocythemia, positive direct Coombs' test, eosinophilia, leukocytosis, leukopenia, prolonged partial thromboplastin time, thrombocytopenic purpura.

Metabolic & Nutritional: Increased SGPT.

Musculo-Skeletal: Myalgia.

Nervous: Hallucination, hyperkinesia, nervousness, somnolence.

Respiratory: Epistaxis, rhinitis.

Skin: Skin moniliasis, urticaria, fungal dermatitis, acne, exfoliative dermatitis, maculopapular rash.

Special Senses: Taste perversion.

Film-coated Tablets (Single dose):
In clinical trials using a s ingle dos e of cefpodoxime proxetil film-coated tablets, 509 patients were treated with the recommended dosage of cefpodoxime (200 mg). There were no deaths or permanent disabilities thought related to drug toxicity in these studies.

Adverse events thought possibly or probably related to cefpodoxime in single-dose clinical trials conducted in the United States were:

Incidence Greater Than 1%:

Nausea	1.4%
Diarrhea	1.2%

Incidence Less Than 1%:
Central Nervous System: Dizziness, headache, syncope.
Dermatologic: Rash.
Genital: Vaginitis.
Gastrointestinal: Abdominal pain.
Psychiatric: Anxiety.

Laboratory Changes
Significant laboratory changes that have been reported in adult and pediatric patients in clinical trials of cefpodoxime proxetil, without regard to drug relationship, were:

Hepatic: Transient increases in AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, bilirubin, and LDH.

Hematologic: Eosinophilia, leukocytosis, lymphocytosis, granulocytosis, basophilia, monocytosis, thrombocytosis, decreased hemoglobin, decreased hematocrit, leukopenia, neutropenia, lymphocytopenia, thrombocytopenia, thrombocythemia, positive Coombs' test, and prolonged PT, and PTT.

Serum Chemistry: Hyperglycemia, hypoglycemia, hypoalbuminemia, hypoproteinemia, hyperkalemia, and hyponatremia.

Renal: Increases in BUN and creatinine.

Most of these abnormalities were transient and not clinically significant.

Post-marketing Experience: The following serious adverse experiences have been reported: allergic reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and serum sickness-like reactions, pseudomembranous colitis, bloody diarrhea with abdominal pain, ulcerative colitis, rectorrhagia with hypotension, anaphylactic shock, acute liver injury, in utero exposure with miscarriage, purpuric nephritis, pulmonary infiltrate with eosinophilia, and eyelid dermatitis.

One death was attributed to pseudomembranous colitis and disseminated intravascular coagulation.

Cephalos porin Class Labeling: In addition to the adverse reactions listed above which have been observed in patients treated with cefpodoxime proxetil, the following adverse reactions and altered laboratory tests have been reported for cephalosporin class antibiotics:

Adverse Reactions and Abnormal Laboratory Tests: Renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, serum sickness-like reaction, hemorrhage, agranulocytosis, and pancytopenia. Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. (See **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE.**) If seizures associated with drug therapy occur, the drug should be discontinued.

Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE
In acute rodent toxicity studies, a single 5 g/kg oral dose produced no adverse effects.

In the event of serious toxic reaction from overdosage, hemodialysis or peritoneal dialysis may aid in the removal of cefpodoxime from the body, particularly if renal function is compromised.

The toxic symptoms following an overdose of beta-lactam antibiotics may include nausea, vomiting, epigastric distress, and diarrhea.

DOSAGE AND ADMINISTRATION

(See INDICATIONS AND USAGE for indicated pathogens .)

FILM-COATED TABLETS: Cefpodoxime proxetil tablets should be administered orally with food to enhance absorption. (See **CLINICAL PHARMACOLOGY.**) The recommended dosages, durations of treatment, and applicable patient population are as described in the following chart:

GRANULES FOR ORAL SUSPENSION: Cefpodoxime proxetil oral suspension may be given without regard to food. The recommended dosages, durations of treatment, and applicable patient populations are as described in the following chart:

ADULTS AND ADOLESCENTS (AGE 12 YEARS AND OLDER):

Type of Infection	Total Daily Dose	Dose Frequency	Duration
Pharyngitis and/or tonsillitis	200 mg	100 mg Q 12 hours	5 to 10 days
Acute community-acquired pneumonia	400 mg	200 mg Q 12 hours	14 days
Acute bacterial exacerbations of chronic bronchitis	400 mg	200 mg Q 12 hours	10 days
Uncomplicated gonorrhea (men and women) and rectal gonococcal infections (women)	200 mg	single dose	
Skin and skin structure	800 mg	400 mg Q 12 hours	7 to 14 days
Acute maxillary sinusitis	400 mg	200 mg Q 12 hours	10 days
Uncomplicated urinary tract infection	200 mg	100 mg Q 12 hours	7 days

ADULTS AND ADOLESCENTS (AGE 12 YEARS AND OLDER):

Type of Infection	Total Daily Dose	Dose Frequency	Duration
Pharyngitis and/or tonsillitis	200 mg	100 mg Q 12 hours	5 to 10 days
Acute community-acquired pneumonia	400 mg	200 mg Q 12 hours	14 days
Uncomplicated gonorrhea (men and women) and rectal gonococcal infections (women)	200 mg	single dose	
Skin and skin structure	800 mg	400 mg Q 12 hours	7 to 14 days
Acute maxillary sinusitis	400 mg	200 mg Q 12 hours	10 days
Uncomplicated urinary tract infection	200 mg	100 mg Q 12 hours	7 days

INFANTS AND PEDIATRIC PATIENTS (AGE 2 MONTHS THROUGH 12 YEARS):

Type of Infection	Total Daily Dose	Dose Frequency	Duration
Acute otitis media	10 mg/kg/day (Max 400 mg/day)	5 mg/kg Q 12 h (Max 200 mg/dose)	5 days
Pharyngitis and/or tonsillitis	10 mg/kg/day (Max 200 mg/day)	5 mg/kg/dose Q 12 h (Max 100 mg/dose)	5 to 10 days
Acute maxillary sinusitis	10 mg/kg/day (Max 400 mg/day)	5 mg/kg Q 12 hours (Max 200 mg/dose)	10 days

Patients with Renal Dysfunction:
For patients with severe renal impairment (<30 mL/min creatinine clearance), the dosing intervals should be increased to Q 24 hours. In patients maintained on hemodialysis, the dose frequency should be 3 times/week after hemodialysis.

When only the serum creatinine level is available, the following formula (based on sex, weight, and age of the patient) may be used to estimate creatinine clearance (mL/min). For this estimate to be valid, the serum creatinine level should represent a steady state of renal function.

Males: (mL/min) = Weight (kg) x (140 - age) / 72 x serum creatinine (mg/100 mL)

Females: (mL/min) = 0.85 x above value

Patients with Cirrhosis:
Cefpodoxime pharmacokinetics in cirrhotic patients (with or without ascites) are similar to those in healthy subjects. Dose adjustment is not necessary in this population.

HOW SUPPLIED

Cefpodoxime Proxetil Tablets, USP 100 mg are light yellowish-orange, elliptical, film-coated tablets debossed with 'C' on one side and '61' on the other side.
Bottles of 100 NDC 69043-006-01

Cefpodoxime Proxetil Tablets , USP 200 mg are coral red, elliptical, film-coated tablets debossed with 'C' on one side and '62' on the other side.
Bottles of 100 NDC 69043-007-01

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in tight, light-resistant container.

Replace cap securely after each opening.

CLINICAL TRIALS

Cystitis
In two double-blind, 2:1 randomized, comparative trials performed in adults in the United States, cefpodoxime proxetil was compared to other beta-lactam antibiotics. In these studies, the following bacterial eradication rates were obtained at 5 to 9 days after therapy:

Pathogen	Cefpodoxime	Cefpodoxime
E. coli	200/243 (82%)	99/123 (80%)
Other pathogens	34/42 (81%)	23/28 (82%)
K. pneumoniae *P. mirabilis* *S. saprophyticus*		
TOTAL	234/285 (82%)	122/151 (81%)

In these studies, clinical cure rates and bacterial eradication rates for cefpodoxime proxetil were comparable to the comparator agents; however, the clinical cure rates and bacteriologic eradication rates were lower than those observed with some other classes of approved agents for cystitis.

Acute Otitis Media Studies
In controlled studies of acute otitis media performed in the United States, where significant rates of beta-lactamase-producing organisms were found, cefpodoxime proxetil was compared to cefixime. In these studies, using very strict evaluability criteria and microbiologic and clinical response criteria at the 4 to 21 day post-therapy follow-up, the following presumptive bacterial eradication/clinical success outcomes (cured and improved) were obtained.

	Cefpodoxime Proxetil	Cefixime
Pathogen	**5 mg/kg Q 12 h x 5 d**	
S. pneumoniae	88/122 (72%)	72/124 (58%)
H. influenzae	50/76 (66%)	61/81 (75%)
M. catarrhalis	22/39 (56%)	23/41 (56%)
S. pyogenes	20/25 (80%)	13/23 (57%)
Clinical success rate	171/254 (67%)	165/258 (64%)

Manufactured for:
Cronus Pharma LLC,
East Brunswick, NJ 08816.
Contact No: 1-844-227-6687
(1-844-2-CRONUS)

Made in India
Code: TS/DRUGS/78/1996
Revised: 08/2018

TAKE TIME.
OBSERVE LABEL
DIRECTIONS.

CEPHALEXIN - CEPHALEXIN CAPSULE

Cronus Pharma LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CEPHALEXIN CAPSULES safely and effectively. See full prescribing information for CEPHALEXIN CAPSULES

CEPHALEXIN capsules, for oral use
Initial U.S. Approval: 1971

INDICATIONS AND USAGE: Cephalexin capsules are a cephalosporin antibacterial drug indicated for the treatment of the following infections caused by susceptible isolates of designated bacteria:

- Respiratory tract infection (1.1)
- Otitis media (1.2)
- Skin and skin structure infections (1.3)
- Bone infections (1.4)
- Genitourinary tract infections (1.5)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cephalexin capsules and other antibacterial drugs, cephalexin capsules should be used only to treat infections that are proven or strongly suspected to be caused by bacteria. (1.6)

DOSAGE AND ADMINISTRATION:

Adults and patients at least 15 years of age	The usual dose is 250 mg every 6 hours, but a dose of 500 mg every 12 hours may be administered (2.1)
Pediatric patients (over 1 year of age)	**Otitis media:** 75 to 100 mg/kg in equally divided doses every 6 hours (2.2) **All other indications:** 25 to 50 mg/kg given in equally divided doses (2.2) **In severe infections:** 50 to 100 mg/kg may be administered in equally divided doses (2.2)

- Duration of therapy ranges from 7 to 14 days depending on the infection type and severity. (2)
- Dosage adjustment is required in patients with severe and end stage renal disease (ESRD) defined as creatinine clearance below 30 mL/min. (2.3)

DOSAGE FORMS AND STRENGTHS:
Capsules: 250 mg and 500 mg (3)

CONTRAINDICATIONS:
Patients with known hypersensitivity to cephalexin or other members of the cephalosporin class of antibacterial drugs. (4)

WARNINGS AND PRECAUTIONS:
- Serious hypersensitivity (anaphylactic) reactions: Prior to use, inquire regarding history of hypersensitivity to betalactam antibacterial drugs. Discontinue the drug if signs or symptoms of an allergic reaction occur and institute supportive measures. (5.1)
- *Clostridium difficile*-associated diarrhea (CDAD): Evaluate if diarrhea occurs. (5.2)
- Direct Coombs' Test Seroconversion: If anemia develops during or after cephalexin therapy, evaluate for drug-induced hemolytic anemia. (5.3)
- Seizure Potential: Use lower dose in patients with renal impairment. (5.4)

ADVERSE REACTIONS: The most common adverse The most common adverse reactions associated with cephalexin include diarrhea, nausea, vomiting, dyspepsia and abdominal pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Cronus Pharma LLC. at 1-844-2-CRONUS (1-844-227-6687) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS:
- Metformin: increased metformin concentrations. Monitor for hypoglycemia. (7.1)
- Probenecid-The renal excretion of cephalexin is inhibited by probenecid. Co-administration of probenecid with cephalexin is not recommended. (7.2)
- Administration of cephalexin may result in a false-positive reaction glucose in the urine. (7.3)

USE IN SPECIFIC POPULATIONS:
- Renal Impairment: Monitor patients longer for toxicity and drug interactions due to delayed clearance. (8.6)

SEE 17 FOR PATIENT COUNSELING INFORMATION.
REVISED 4/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Respiratory Tract Infections Cephalexin capsules are indicated for the treatment of respiratory tract infections caused by susceptible isolates of *Streptococcus pneumoniae* and *Streptococcus pyogenes*.

1.2 Otitis Media Cephalexin capsules are indicated for the treatment of otitis media caused by susceptible isolates of *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Streptococcus pyogenes*, and *Moraxella catarrhalis*.

1.3 Skin and Skin Structure Infections Cephalexin capsules are indicated for the treatment of skin and skin structure infections caused by susceptible isolates of the following Gram-positive bacteria: *Staphylococcus aureus* and *Streptococcus pyogenes*.

1.4 Bone Infections Cephalexin capsules are indicated for the treatment of bone infections caused by susceptible isolates of *Staphylococcus aureus* and *Proteus mirabilis*.

1.5 Genitourinary Tract Infections Cephalexin capsules are indicated for the treatment of genitourinary tract infections, including acute prostatitis, caused by susceptible isolates of *Escherichia coli, Proteus mirabilis,* and *Klebsiella pneumoniae.*

1.6 Usage To reduce the development of drug-resistant bacteria and maintain the effectiveness of cephalexin capsules and other antibacterial drugs, cephalexin capsules should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information is available, this information should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Adults and Pediatric Patients at Least 15 Years of Age The usual dose of oral cephalexin capsules is 250 mg every 6 hours, but a dose of 500 mg every 12 hours may be administered. Treatment is administered for 7 to 14 days.

For more severe infections larger doses of oral cephalexin capsules may be needed, up to 4 grams daily in two to four equally divided doses.

2.2 Pediatric Patients (over 1 year of age) The recommended total daily dose of oral

cephalexin capsules for pediatric patients is 25 to 50 mg/kg given in equally divided doses for 7 to 14 days. In the treatment of β-hemolytic streptococcal infections, duration of at least 10 days is recommended. In severe infections, a total daily dose of 50 to 100 mg/kg may be administered in equally divided doses.

For the treatment of otitis media, the recommended daily dose is 75 to 100 mg/kg given in equally divided doses.

2.3 Dosage Adjustments in Adult and Pediatric Patients at Least 15 Years of Age with Renal Impairment Administer the following dosing regimens for cephalexin capsules to patients with renal impairment *[see Warnings and Precautions (5.4)* and *Use in Specific Populations (8.6)].*

TABLE 1. RECOMMENDED DOSE REGIMEN FOR PATIENTS WITH RENAL IMPAIRMENT

Renal function	Dose regimen recommendation
Creatinine clearance > 60 mL/min	No dose adjustment
Creatinine clearance 30 to 59 mL/min	No dose adjustment; maximum daily dose should not exceed 1 g
Creatinine clearance 15 to 29 mL/min	250 mg, every 8 hours or every 12 hours
Creatinine clearance 5 to 14 mL/min not yet on dialysis*	250 mg, every 24 hours
Creatinine clearance 1 to 4 mL/min not yet on dialysis*	250 mg, every 48 hours or every 60 hours

*There is insufficient information to make dose adjustment recommendations in patients on hemodialysis.

3 DOSAGE FORMS AND STRENGTHS

250 mg capsules: Dark green opaque/white size “2” hard gelatin capsule filled with off white granular powder and imprinted with “A 42” on dark green opaque cap and “250 mg” on white body with black ink.

500 mg capsules: Dark green opaque/light green opaque size “0” hard gelatin capsule filled with off white granular powder and imprinted with “A 43” on dark green opaque cap and “500 mg” on light green opaque body with black ink.

4 CONTRAINDICATIONS

Cephalexin capsules are contraindicated in patients with known hypersensitivity to cephalexin or other members of the cephalosporin class of antibacterial drugs.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions Allergic reactions in the form of rash, urticaria, angioedema, anaphylaxis, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis have been reported with the use of cephalexin. Before therapy with cephalexin is instituted, inquire whether the patient has a history of hypersensitivity reactions to cephalexin, cephalosporins, penicillins, or other drugs. Crosshypersensitivity among beta-lactam antibacterial drugs may occur in up to 10% of patients with a history of penicillin allergy.

If an allergic reaction to cephalexin occurs, discontinue the drug and institute appropriate treatment.

5.2 Clostridium difficile-Associated Diarrhea *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including cephalexin, and may range in severity from mild diarrhea to fatal colitis.Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxinproducing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.3 Direct Coombs’ Test Seroconversion Positive direct Coombs’ tests have been reported during treatment with the cephalosporin antibacterial drugs including cephalexin. Acute intravascular hemolysis induced by cephalexin therapy has been reported. If anemia develops during or after cephalexin therapy, perform a diagnostic work-up for drug-induced hemolytic anemia, discontinue cephalexin and institute appropriate therapy.

5.4 Seizure Potential Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. If seizures occur, discontinue cephalexin. Anticonvulsant therapy can be given if clinically indicated.

5.5 Prolonged Prothrombin Time Cephalosporins may be associated with prolonged prothrombin time. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antibacterial therapy, and patients receiving anticoagulant therapy. Monitor prothrombin time in patients at risk and manage as indicated.

5.6 Development of Drug-Resistant Bacteria Prescribing cephalexin in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Prolonged use of cephalexin may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

6 ADVERSE REACTIONS

The following serious events are described in greater detail in the Warning and Precautions section:

- Hypersensitivity reactions *[see Warning and Precautions (5.1)]*
- *Clostridium difficile*-associated diarrhea *[see Warnings and Precautions (5.2)]*
- Direct Coombs’ Test Seroconversion *[see Warnings and Precautions (5.3)]*
- Seizure Potential *[see Warnings and Precautions (5.4)]*
- Effect on Prothrombin Activity *[see Warnings and Precautions (5.5)]*
- Development of Drug-Resistant Bacteria *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, the most frequent adverse reaction was diarrhea. Nausea and vomiting, dyspepsia, gastritis, and abdominal pain have also occurred. As with penicillins and other cephalosporins, transient hepatitis and cholestatic jaundice have been reported.

Other reactions have included hypersensitivity reactions, genital and anal pruritus, genital candidiasis, vaginitis and vaginal discharge, dizziness, fatigue, headache, agitation, confusion, hallucinations, arthralgia, arthritis, and joint disorder. Reversible interstitial nephritis has been reported. Eosinophilia, neutropenia, thrombocytopenia, hemolytic anemia, and slight elevations in aspartate transaminase (AST) and alanine transaminase (ALT) have been reported.

In addition to the adverse reactions listed above that have been observed in patients treated with cephalexin, the following adverse reactions and other altered laboratory tests have been reported for cephalosporin class antibacterial drugs:

Other Adverse Reactions: Fever, colitis, aplastic anemia, hemorrhage, renal dysfunction, and toxic nephropathy.

Altered Laboratory Tests: Prolonged prothrombin time, increased blood urea nitrogen (BUN), increased creatinine, elevated alkaline phosphatase, elevated bilirubin, elevated lactate dehydrogenase (LDH), pancytopenia, leukopenia, and agranulocytosis.

7 DRUG INTERACTIONS

7.1 Metformin Administration of cephalexin with metformin results in increased plasma metformin concentrations and decreased renal clearance of metformin.

Careful patient monitoring and dose adjustment of metformin is recommended in patients concomitantly taking cephalexin and metformin *[see Clinical Pharmacology (12.3)].*

7.2 Probenecid The renal excretion of cephalexin is inhibited by probenecid. Co-administration of probenecid with cephalexin is not recommended.

7.3 Interaction with Laboratory or Diagnostic Testing A false-positive reaction may occur when testing for the presence of glucose in the urine using Benedict’s solution or Fehling’s solution.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary Available data from published epidemiologic studies and pharmacovigilance case reports over several decades with cephalosporin use, including cephalexin use in pregnant women have not established drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data).*

Animal reproduction studies with mice and rats using oral doses of cephalexin that are 0.6- and 1.2- times the maximum recommended human dose (MRHD) based on body surface area during organogenesis revealed no evidence of harm to the fetus (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data *Human Data*

While available studies cannot definitively establish the absence of risk, published data from epidemiologic studies and postmarketing case reports over several decades have not identified a consistent association with cephalosporin use, including cephalexin, during pregnancy, and major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Available studies have methodologic limitations, including small sample size, retrospective data collection, and inconsistent comparator groups.

Animal Data

In animal reproduction studies, pregnant mice and rats administered oral cephalexin doses of 250 or 500 mg/kg/day (approximately 0.6 and 1.2 times the MRHD) based on body surface area, respectively during the period of organogenesis showed no adverse effects on embryofetal development.

In a pre-and post-natal developmental toxicity study, pregnant rats that received oral doses of 250 or 500 mg/kg/day of cephalexin from Day 15 of pregnancy to litter Day 21 showed no adverse effects on parturition, litter size, or growth of offspring.

8.2 Lactation

Risk Summary Data from a published clinical lactation study reports that cephalexin is present in human milk. The Relative Infant Dose (RID) is considered to be <1% of the maternal weight adjusted dose. There are no data on the effects of cephalexin on the breastfed child or on milk production.

The development of health benefits of breastfeeding should be considered along with the mother’s clinical need for cephalexin and any potential adverse effects on the breastfed child from cephalexin or from the underlying maternal condition.

8.4 Pediatric Use The safety and effectiveness of cephalexin in pediatric patients was established in clinical trials for the dosages described in the dosage and administration section *[see Dosage and Administration (2.2)].*

8.5 Geriatric Use Of the 701 subjects in 3 published clinical studies of cephalexin, 433 (62%) were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

This drug is substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection *[see Warnings and Precautions (5.4)].*

8.6 Renal Impairment Cephalexin should be administered with careful monitoring in the presence of renal impairment (creatinine clearance < 30 mL/min, with or without dialysis). Under such conditions, careful clinical observation and laboratory studies renal function monitoring should be conducted because safe dosage may be lower than that usually recommended *[see Dosage and Administration (2.3)].* Monitor patients longer for toxicity and drug interactions due to delayed clearance.

10 OVERDOSAGE

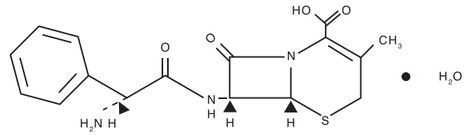
Symptoms of oral overdose may include nausea, vomiting, epigastric distress, diarrhea, and hematuria. In the event of an overdose, institute general supportive measures.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of cephalexin.

11 DESCRIPTION

Cephalexin capsules, USP is a semisynthetic cephalosporin antibacterial drug intended for oral administration. It is 7-(D-α-Amino-α-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid monohydrate. Cephalexin has the molecular formula $C_{16}H_{17}N_3O_4S{\cdot}H_2O$ and the molecular weight is 365.41.

Cephalexin has the following structural formula:



Each capsule contains cephalexin monohydrate equivalent to 250 mg or 500 mg of cephalexin. The capsules also contain the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, D&C Yellow No. 10, FD&C Blue No. 1, FD&C Yellow No. 6, gelatin, magnesium stearate, titanium dioxide, and sodium lauryl sulfate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action Cephalexin is a cephalosporin antibacterial drug *[see Microbiology (12.4)].*

12.3 Pharmacokinetics

Absorption: Cephalexin is acid stable and may be given without regard to meals. Following doses of 250 mg, 500 mg, and 1 g, average peak serum levels of approximately 9, 18, and 32 mcg/mL, respectively, were obtained at 1 hour. Serum levels were detectable 6 hours after administration (at a level of detection of 0.2 mcg/mL).

Distribution: Cephalexin is approximately 10% to 15% bound to plasma proteins.

Excretion: Cephalexin is excreted in the urine by glomerular filtration and tubular secretion. Studies showed that over 90% of the drug was excreted unchanged in the urine within 8 hours. During this period, peak urine concentrations following the 250 mg, 500 mg, and 1 g doses were approximately 1000, 2200, and 5000 mcg/mL respectively.

Drug Interactions: In healthy subjects given single 500 mg doses of cephalexin and metformin, plasma metformin mean C_{MAX} and AUC increased by an average of 34% and 24%, respectively, and metformin mean renal clearance decreased by 14%. No information is available about the interaction of cephalexin and metformin following multiple doses of either drug.

12.4 Microbiology

Mechanism of Action Cephalexin is a bactericidal agent that acts by the inhibition of bacterial cell-wall synthesis.

Resistance Methicillin-resistant staphylococci and most isolates of enterococci are resistant to cephalexin. Cephalexin is not active against most isolates of *Enterobacter spp., Morganella morganii*, and *Proteus vulgaris*. Cephalexin has no activity against P*seudomonas spp., or Acinetobacter calcoaceticus.* Penicillin-resistant Streptococcus pneumoniae is usually cross-resistant to beta-lactam antibacterial drugs.

Antimicrobial Activity Cephalexin has been shown to be active against most isolates of the following bacteria both in vitro and in clinical infections *[see Indications and Usage (1)].*

Gram-positive bacteria

Staphylococcus aureus (methicillin-susceptible isolates only)
Streptococcus pneumoniae (penicillin-susceptible isolates)

Gram-negative bacteria
Escherichia coli
Haemophilus influenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Proteus mirabilis

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Lifetime studies in animals have not been performed to evaluate the carcinogenic potential of cephalexin. Tests to determine the mutagenic potential of cephalexin have not been performed. In male and female rats, fertility and reproductive performance were not affected by cephalexin oral doses up to 1.5 times the highest recommended human dose based upon body surface area.

16 HOW SUPPLIED/STORAGE AND HANDLING

Cephalexin capsules, USP are available in:

250 mg Capsule Dark green opaque/white size “2” hard gelatin capsule filled with off white granular powder and imprinted with “A 42” on dark green opaque cap and “250 mg” on white body with black ink.

Bottles of 100	NDC 69043-008-01
Bottles of 500	NDC 69043-008-05

500 mg Capsule Dark green opaque/light green opaque size “0” hard gelatin capsule filled with off white granular powder and imprinted with “A 43” on dark green opaque cap and “500 mg” on light green opaque body with black ink.

Bottles of 100	NDC 69043-009-01
Bottles of 500	NDC 69043-009-05

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container.

17 PATIENT COUNSELING INFORMATION

Allergic Reactions Advise patients that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. Ask the patient about any previous hypersensitivity reactions to cephalexin, other beta-lactams (including cephalosporins) or other allergens (5.1)

Diarrhea Advise patients that diarrhea is a common problem caused by antibacterial drugs and usually resolves when the drug is discontinued. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, advise patients to contact their healthcare provider.

Antibacterial Resistance Counsel patients that antibacterial drugs including cephalexin, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When cephalexin is prescribed to treat a bacterial infection, tell patients that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by cephalexin or other antibacterial drugs in the future.

Manufactured for:
CRONUS PHARMA LLC
2 Tower Center Blvd, Suite - 1101A
East Brunswick, NJ 08816.
USA

Made in India
Code: TS/DRUGS/78/1996
Issued: 04/2019

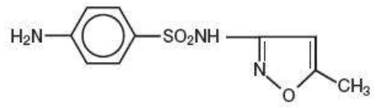
TAKE TIME.
OBSERVE LABEL
DIRECTIONS.

SULFAMETHOXAZOLE AND TRIMETHOPRIM TABLETS, USP

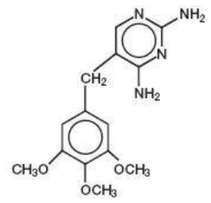
RX only
To reduce the development of drug-resistant bacteria and maintain the effectiveness of sulfamethoxazole and trimethoprim tablets and other antibacterial drugs, sulfamethoxazole and trimethoprim tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION: Sulfamethoxazole and trimethoprim is a synthetic antibacterial combination product available in DS (double strength) tablets, each containing 800 mg sulfamethoxazole and 160 mg trimethoprim; in tablets, each containing 400 mg sulfamethoxazole and 80 mg trimethoprim for oral administration.

Sulfamethoxazole is *N*¹-(5-methyl-3-isoxazolyl)sulfanilamide; the molecular formula is $C_{10}H_{11}N_3O_3S$. It is a white to off-white, practically odorless, crystalline powder, tasteless compound with a molecular weight of 253.28 and the following structural formula:



Trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine; the molecular formula is $C_{14}H_{18}N_4O_3$. It is a white or cream-colored crystals or crystalline powder with a molecular weight of 290.3 and the following structural formula:



Inactive Ingredients: Docusate sodium, magnesium stearate, pregelatinized starch (maize), sodium benzoate, and sodium starch glycolate.

CLINICAL PHARMACOLOGY: Sulfamethoxazole and trimethoprim is rapidly absorbed following oral administration. Both sulfamethoxazole and trimethoprim exist in the blood as unbound, protein-bound and metabolized forms; sulfamethoxazole also exists as the conjugated form. Sulfamethoxazole is metabolized in humans to at least 5 metabolites: the N_4-acetyl-, N_4-hydroxy-, 5-methylhydroxy-, N_4-acetyl-5-methylhydroxy- sulfamethoxazole metabolites, and an N-glucuronide conjugate. The formulation of N_4-hydroxy metabolite is mediated *via* CYP2C9.

Trimethoprim is metabolized *in vitro* to 11 different metabolites, of which, five are glutathione adducts and six are oxidative metabolites, including the major metabolites, 1- and 3-oxides and the 3- and 4-hydroxy derivatives.

The free forms of sulfamethoxazole and trimethoprim are considered to be the therapeutically active forms.

In vitro studies suggest that trimethoprim is a substrate of P-glycoprotein, OCT1 and OCT2, and that sulfamethoxazole is not a substrate of P-glycoprotein.

Approximately 70% of sulfamethoxazole and 44% of trimethoprim are bound to plasma proteins. The presence of 10 mg percent sulfamethoxazole in plasma decreases the protein binding of trimethoprim by an insignificant degree; trimethoprim does not influence the protein binding of sulfamethoxazole.

Peak blood levels for the individual components occur 1 to 4 hours after oral administration. The mean serum half-lives of sulfamethoxazole and trimethoprim are 10 and 8 to 10 hours, respectively. However, patients with severely impaired renal function exhibit an increase in the half-lives of both components, requiring dosage regimen adjustment **(see DOSAGE AND ADMINISTRATION section)**. Detectable amounts of sulfamethoxazole and trimethoprim are present in the blood 24 hours after drug administration. During administration of 800 mg sulfamethoxazole and 160 mg trimethoprim b.i.d., the mean steady-state plasma concentration of trimethoprim was 1.72 mcg/mL. The steady-state mean plasma levels of free and total sulfamethoxazole were 57.4 mcg/mL and 68 mcg/mL, respectively. These steady-state levels were achieved after three days of drug administration[1]. Excretion of sulfamethoxazole and trimethoprim is primarily by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both sulfamethoxazole and trimethoprim are considerably higher than are the concentrations in the blood. The average percentage of the dose recovered in urine from 0 to 72 hours after a single oral dose of sulfamethoxazole and trimethoprim is 84.5% for total sulfonamide and 66.8% for free trimethoprim. Thirty percent of the total sulfonamide is excreted as free sulfamethoxazole, with the remaining as N_4-acetylated metabolite[2]. When administered together as sulfamethoxazole and trimethoprim, neither sulfamethoxazole nor trimethoprim affects the urinary excretion pattern of the other.

Both sulfamethoxazole and trimethoprim distribute to sputum, vaginal fluid and middle ear fluid; trimethoprim also distributes to bronchial secretion, and both pass the placental barrier and are excreted in human milk.

Pharmacokinetics in Pediatric Patients: A simulation conducted with data from a pharmacokinetic study in 153 infants and children demonstrated that mean steady state AUC and maximum plasma concentration of trimethoprim and sulfamethoxazole would be comparable between pediatric patients 2 months to 18 years receiving 8/40 (trimethoprim/ sulfamethoxazole) mg/kg/day divided every 12 hours and adult patients receiving 320/1600 (trimethoprim/ sulfamethoxazole) mg/day.

Pharmacokinetics in Geriatric Patients: The pharmacokinetics of sulfamethoxazole 800 mg and trimethoprim 160 mg were studied in 6 geriatric subjects (mean age: 78.6 years) and 6 young healthy subjects (mean age: 29.3 years) using a non-U.S. approved formulation. Pharmacokinetic values for sulfamethoxazole in geriatric subjects were similar to those observed in young adult subjects. The mean renal clearance of trimethoprim was significantly lower in geriatric subjects compared with young adult subjects (19 mL/h/kg vs. 55 mL/h/kg). However, after normalizing by body weight, the apparent total body clearance of trimethoprim was on average 19% lower in geriatric subjects compared with young adult subjects[3].

MICROBIOLOGY
MECHANISM OF ACTION Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid (PABA). Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Thus, sulfamethoxazole and trimethoprim blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

RESISTANCE *In vitro* studies have shown that bacterial resistance develops more slowly with both sulfamethoxazole and trimethoprim in combination than with either sulfamethoxazole or trimethoprim alone.

ANTIMICROBIAL ACTIVITY Sulfamethoxazole and trimethoprim have been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobic gram-positive bacteria:
Streptococcus pneumoniae

Aerobic gram-negative bacteria:
Escherichia coli (including susceptible enterotoxigenic strains implicated in traveler's diarrhea)
Klebsiella species
Enterobacter species
Haemophilus influenzae
Morganella morganii
Proteus mirabilis
Proteus vulgaris
Shigella flexneri
Shigella sonnei

Other Microorganisms:
Pneumocystis jirovecii

SUSCEPTIBILITY TESTING For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

INDICATIONS AND USAGE: To reduce the development of drug-resistant bacteria and maintain the effectiveness of sulfamethoxazole and trimethoprim tablets and other antibacterial drugs, sulfamethoxazole and trimethoprim tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to empiric selection of therapy.

Urinary Tract Infections: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella species, Enterobacter species, Morganella morganii, Proteus mirabilis and Proteus vulgaris*. It is recommended initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

Acute Otitis Media: For the treatment of acute otitis media in pediatric patients due to susceptible strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* when in the judgment of the physician sulfamethoxazole and trimethoprim tablets offers some advantage over the use of other antimicrobial agents. To date, there are limited data on the safety of repeated use of sulfamethoxazole and trimethoprim tablets in pediatric patients under two years of age. Sulfamethoxazole and trimethoprim tablets are not indicated for prophylactic or prolonged administration in otitis media at any age.

Acute Exacerbations of Chronic Bronchitis in Adults: For the treatment of acute exacerbations of chronic bronchitis due to susceptible strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* when a physician deems that sulfamethoxazole and trimethoprim tablets could offer some advantage over the use of a single antimicrobial agent.

Shigellosis: For the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Pneumocystis jirovecii Pneumonia: For the treatment of documented *Pneumocystis jirovecii* pneumonia and for prophylaxis against *P. jirovecii pneumonia* in individuals who are immunosuppressed and considered to be at an increased risk of developing *P. jirovecii* pneumonia.

Traveler's Diarrhea in Adults: For the treatment of traveler's diarrhea due to susceptible strains of enterotoxigenic *E. coli.*

CONTRAINDICATIONS:
Sulfamethoxazole and trimethoprim tablets are contraindicated in patients with a known hypersensitivity to trimethoprim or sulfonamides, in patients with a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulfonamides, and in patients with documented megaloblastic anemia due to folate deficiency.

Sulfamethoxazole and trimethoprim tablets are contraindicated in pediatric patients less than 2 months of age. Sulfamethoxazole and trimethoprim tablets are also contraindicated in patients with marked hepatic damage or with severe renal insufficiency when renal function status cannot be monitored.

WARNINGS:
EMBRYOFETAL TOXICITY Some epidemiologic studies suggest that exposure to sulfamethoxazole and trimethoprim during pregnancy may be associated with an increased risk of congenital malformations, particularly neural tube defects, cardiovascular malformations, urinary tract defects, oral clefts, and club foot. If sulfamethoxazole and trimethoprim is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be advised of the potential hazards to the fetus.

HYPERSENSITIVITY AND OTHER FATAL REACTIONS Fatalities associated with the administration of sulfonamides, although rare, have occurred due to severe reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias.

Sulfonamides, including sulfonamide-containing products such as sulfamethoxazole and trimethoprim, should be discontinued at the first appearance of skin rash or any sign of adverse reaction. In rare instances, a skin rash may be followed by a more severe reaction, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis, and serious blood disorders **(see PRECAUTIONS).** Clinical signs, such as rash, sore throat, fever, arthralgia, pallor, purpura or jaundice may be early indications of serious reactions.

Cough, shortness of breath, and pulmonary infiltrates are hypersensitivity reactions of the respiratory tract that have been reported in association with sulfonamide treatment.

THROMBOCYTOPENIA Sulfamethoxazole and trimethoprim-induced thrombocytopenia may be an immunemediated disorder. Severe cases of thrombocytopenia that are fatal or life threatening have been reported. Thrombocytopenia usually resolves within a week upon discontinuation of sulfamethoxazole and trimethoprim.

STREPTOCOCCAL INFECTIONS AND RHEUMATIC FEVER The sulfonamides should not be used for treatment of group A β-hemolytic streptococcal infections. In an established infection, they will not eradicate the streptococcus and, therefore, will not prevent sequelae such as rheumatic fever.

CLOSTRIDIOIDES DIFFICILE ASSOCIATED DIARRHEA *Clostridioides difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including sulfamethoxazole and trimethoprim, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

ADJUNCTIVE TREATMENT WITH LEUCOVORIN FOR PNEUMOCYSTIS JIROVECII PNEUMONIA Treatment failure and excess mortality were observed when trimethoprim-sulfamethoxazole was used concomitantly with leucovorin for the treatment of HIV positive patients with *Pneumocystis jirovecii* pneumonia in a randomized placebo controlled trial[4]. Co-administration of trimethoprim-sulfamethoxazole and leucovorin during treatment of *Pneumocystis jirovecii* pneumonia should be avoided.

PRECAUTIONS:
DEVELOPMENT OF DRUG RESISTANT BACTERIA Prescribing sulfamethoxazole and trimethoprim tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

FOLATE DEFICIENCY Sulfamethoxazole and trimethoprim should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency (e.g., the elderly, chronic alcoholics, patients receiving anticonvulsant therapy, patients with malabsorption syndrome, and patients in malnutrition states) and to those with severe allergies or bronchial asthma.

Hematological changes indicative of folic acid deficiency may occur in elderly patients or in patients with preexisting folic acid deficiency or kidney failure. These effects are reversible by folinic acid therapy.

HEMOLYSIS In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction is frequently dose-related **(see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).**

HYPOGLYCEMIA Cases of hypoglycemia in non-diabetic patients treated with sulfamethoxazole and trimethoprim are seen rarely, usually occurring after a few days of therapy. Patients with renal dysfunction, liver disease, malnutrition or those receiving high doses ofsulfamethoxazole and trimethoprim are particularly at risk.

PHENYLALANINE METABOLISM Trimethoprim has been noted to impair phenylalanine metabolism, but this is of no significance in phenylketonuric patients on appropriate dietary restriction.

PORPHYRIA AND HYPOTHYROIDISM As with all drugs containing sulfonamides, caution is advisable in patients with porphyria or thyroid dysfunction.

USE IN THE TREATMENT OF AND PROPHYLAXIS FOR PNEUMOCYSTIS JIROVECII PNEUMONIA IN PATIENTS WITH ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS): AIDS patients may not tolerate or respond to sulfamethoxazole and trimethoprim in the same manner as non-AIDS patients. The incidence of side effects, particularly rash, fever, leukopenia and elevated aminotransferase (transaminase) values, with sulfamethoxazole and trimethoprim therapy in AIDS patients who are being treated for *P. jirovecii* pneumonia has been reported to be greatly increased compared with the incidence normally associated with the use of sulfamethoxazole and trimethoprim in non-AIDS patients. Adverse effects are generally less severe in patients receiving sulfamethoxazole and trimethoprim for prophylaxis. A history of mild intolerance to sulfamethoxazole and trimethoprim in AIDS patients does not appear to predict intolerance of subsequent secondary prophylaxis[5]. However, if a patient develops skin rash or any sign of adverse reaction, therapy with sulfamethoxazole and trimethoprim should be reevaluated **(see WARNINGS).**

Co-administration of sulfamethoxazole and trimethoprim and leucovorin should be avoided with *P. jirovecii* pneumonia **(see WARNINGS).**

ELECTROLYTE ABNORMALITIES High dosage of trimethoprim, as used in patients with *P. jirovecii* pneumonia, induces a progressive but reversible increase of serum potassium concentrations in a substantial number of patients. Even treatment with recommended doses may cause hyperkalemia when trimethoprim is administered to patients with underlying disorders of potassium metabolism, with renal insufficiency, or if drugs known to induce hyperkalemia are given concomitantly. Close monitoring of serum potassium is warranted in these patients.

Severe and symptomatic hyponatremia can occur in patients receiving sulfamethoxazole and trimethoprim, particularly for the treatment of *P. jirovecii* pneumonia. Evaluation for hyponatremia and appropriate correction is necessary in symptomatic patients to prevent life-threatening complications.

During treatment, adequate fluid intake and urinary output should be ensured to prevent crystalluria. Patients who are "slow acetylators" may be more prone to idiosyncratic reactions to sulfonamides.

INFORMATION FOR PATIENTS: Patients should be counseled that antibacterial drugs including sulfamethoxazole and trimethoprim tablets should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When sulfamethoxazole and trimethoprim tablets are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by sulfamethoxazole and trimethoprim tablets or other antibacterial drugs in the future.

Patients should be instructed to maintain an adequate fluid intake in order to prevent crystalluria and stone formation.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

LABORATORY TESTS: Complete blood counts should be done frequently in patients receiving sulfamethoxazole and trimethoprim; if a significant reduction in the count of any formed blood element is noted, sulfamethoxazole and trimethoprim should be discontinued. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

DRUG INTERACTIONS:
POTENTIAL FOR SULFAMETHOXAZOLE AND TRIMETHOPRIM TO AFFECT OTHER DRUGS Trimethoprim is an inhibitor of CYP2C8 as well as OCT2 transporter. Sulfamethoxazole is an inhibitor of CYP2C9. Caution is recommended when sulfamethoxazole and trimethoprim is co-administered with drugs that are substrates of CYP2C8 and 2C9 or OCT2.

In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported.

It has been reported that sulfamethoxazole and trimethoprim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin (a CYP2C9 substrate). This interaction should be kept in mind when sulfamethoxazole and trimethoprim is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

Sulfamethoxazole and trimethoprim may inhibit the hepatic metabolism of phenytoin (a CYP2C9 substrate). Sulfamethoxazole and trimethoprim, given at a common clinical dosage, increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect.

Sulfonamides can also displace methotrexate from plasma protein binding sites and can compete with the renal transport of methotrexate, thus increasing free methotrexate concentrations.

There have been reports of marked but reversible nephrotoxicity with coadministration of sulfamethoxazole and trimethoprim and cyclosporine in renal transplant recipients

Increased digoxin blood levels can occur with concomitant sulfamethoxazole and trimethoprim therapy, especially in elderly patients. Serum digoxin levels should be monitored.

Increased sulfamethoxazole blood levels may occur in patients who are also receiving indomethacin.

Occasional reports suggest that patients receiving pyrimethamine as malaria prophylaxis in doses exceeding 25 mg weekly may develop megaloblastic anemia if sulfamethoxazole and trimethoprim is prescribed.

The efficacy of tricyclic antidepressants can decrease when coadministered with sulfamethoxazole and trimethoprim.

Sulfamethoxazole and trimethoprim potentiates the effect of oral hypoglycemics that are metabolized by CYP2C8 (e.g., pioglitazone, repaglinide, and rosiglitazone) or CYP2C9 (e.g., glipizide and glyburide) or eliminated renally *via* OCT2 (e.g., metformin). Additional monitoring of blood glucose may be warranted.

In the literature, a single case of toxic delirium has been reported after concomitant intake of sulfamethoxazole and trimethoprim and amantadine (an OCT2 substrate). Cases of interactions with other OCT2 substrates, memantine and metformin, have also been reported.

In the literature, three cases of hyperkalemia in elderly patients have been reported after concomitant intake of sulfamethoxazole and trimethoprim and an angiotensin converting enzyme inhibitor[6,7].

DRUG/LABORATORY TEST INTERACTIONS: Sulfamethoxazole and trimethoprim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by a radioimmunoassay (RIA).

The presence of sulfamethoxazole and trimethoprim may also interfere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in overestimations of about 10% in the range of normal values.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: *Carcinogenesis*: Sulfamethoxazole was not carcinogenic when assessed in a 26-week tumorigenic mouse (Tg-rasH2) study at doses up to 400 mg/kg/day sulfamethoxazole; equivalent to 2.4-fold the human systemic exposure (at a daily dose of 800 mg sulfamethoxazole *b.i.d.*).

Mutagenesis: *In vitro* reverse mutation bacterial tests according to the standard protocol have not been performed with sulfamethoxazole and trimethoprim in combination. An *in vitro* chromosomal aberration test in human lymphocytes with sulfamethoxazole and trimethoprim was negative. In *in vitro* and *in vivo* tests in animal species, sulfamethoxazole and trimethoprim did not damage chromosomes. In vivo micronucleus assays were positive following oral administration of sulfamethoxazole and trimethoprim.Observations of leukocytes obtained from patients treated with sulfamethoxazole and trimethoprim revealed no chromosomal abnormalities.

Sulfamethoxazole alone was positive in an *in vitro* reverse mutation bacterial assay and in *in vitro* micronucleus assays using cultured human lymphocytes.

Trimethoprim alone was negative in *in vitro* reverse mutation bacterial assays and in *in vitro* chromosomal aberration assays with Chinese Hamster ovary or lung cells with or without S9 activation. In *in vitro* Comet, micronucleus and chromosomal damage assays using cultured human lymphocytes, trimethoprim was positive. In mice following oral administration of trimethoprim, no DNA damage in Comet assays of liver, kidney, lung, spleen, or bone marrow was recorded.

Impairment of Fertility: No adverse effects on fertility or general reproductive performance were observed in rats given oral dosages as high as 350 mg/kg/day sulfamethoxazole plus 70 mg/kg/day trimethoprim, doses roughly two times the recommended human daily dose on a body surface area basis.

Pregnancy: While there are no large, well-controlled studies on the use of sulfamethoxazole and trimethoprim in pregnant women, Brumfitt and Pursell,[8] in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or sulfamethoxazole and trimethoprim. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving sulfamethoxazole and trimethoprim. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral sulfamethoxazole and trimethoprim at the time of conception or shortly thereafter

Because sulfamethoxazole and trimethoprim may interfere with folic acid metabolism, sulfamethoxazole and trimethoprim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data: While there are no large prospective, well controlled studies in pregnant women and their babies, some retrospective epidemiologic studies suggest an association between first trimester exposure to sulfamethoxazole and trimethoprim with an increased risk of congenital malformations, particularly neural tube defects, cardiovascular abnormalities, urinary tract defects, oral clefts, and club foot. These studies, however, were limited by the small number of exposed cases and the lack of adjustment for multiple statistical comparisons and confounders. These studies are further limited by recall, selection, and information biases, and by limited generalizability of their findings. Lastly, outcome measures varied between studies, limiting cross-study comparisons. Alternatively, other epidemiologic studies did not detect statistically significant associations between sulfamethoxazole and trimethoprim exposure and specific malformations

Animal Data: In rats, oral doses of either 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratologic effects manifested mainly as cleft palates. These doses are approximately 5 and 6 times the recommended human total daily dose on a body surface area basis. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. In some rabbit studies, an overall increase in fetal loss (dead and resorbed conceptuses) was associated with doses of trimethoprim 6 times the human therapeutic dose based on body surface area.

Nonteratogenic Effects: See CONTRAINDICATIONS section.

NURSING MOTHERS: Levels of trimethoprim and sulfamethoxazole in breast milk are approximately 2 to 5% of the recommended daily dose for infants over 2 months of age. Caution should be exercised when sulfamethoxazole and trimethoprim is administered to a nursing woman, especially when breastfeeding, jaundiced, ill, stressed, or premature infants because of the potential risk of bilirubin displacement and kernicterus.

PEDIATRIC USE: Sulfamethoxazole and trimethoprim is contraindicated for infants younger than 2 months of age (see INDICATIONS and CONTRAINDICATIONS sections).

GERIATRIC USE: Clinical studies of sulfamethoxazole and trimethoprim did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

There may be an increased risk of severe adverse reactions in elderly patients, particularly when complicating conditions exist, e.g., impaired kidney and/or liver function, possible folate deficiency, or concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression (see WARNINGS and ADVERSE REACTIONS sections), a specific decrease in platelets (with or without purpura), and hyperkalemia are the most frequently reported severe adverse reactions in elderly patients. In those concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Increased digoxin blood levels can occur with concomitant sulfamethoxazole and trimethoprim therapy, especially in elderly patients. Serum digoxin levels should be monitored. Hematological changes indicative of folic acid deficiency may occur in elderly patients. These effects are reversible by folinic acid therapy. Appropriate dosage adjustments should be made for patients with impaired kidney function and duration of use should be as short as possible to minimize risks of undesired reactions (see DOSAGE AND ADMINISTRATION section). The trimethoprim component of sulfamethoxazole and trimethoprim may cause hyperkalemia when administered to patients with underlying disorders of potassium metabolism, with renal insufficiency or when given concomitantly with drugs known to induce hyperkalemia, such as angiotensin converting enzyme inhibitors. Close monitoring of serum potassium is warranted in these patients. Discontinuation of sulfamethoxazole and trimethoprim treatment is recommended to help lower potassium serum levels. Sulfamethoxazole and trimethoprim tablets contain 0.45 mg sodium (0.02 mEq) of sodium per tablet. Sulfamethoxazole and trimethoprim DS tablets contain 0.9 mg (0.04 mEq) of sodium per tablet.

Pharmacokinetics parameters for sulfamethoxazole were similar for geriatric subjects and younger adult subjects. The mean maximum serum trimethoprim concentration was higher and mean renal clearance of trimethoprim was lower in geriatric subjects compared with younger subjects (see CLINICAL PHARMACOLOGY: Geriatric Pharmacokinetics).

ADVERSE REACTIONS: The most common adverse effects are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS SECTION).**

Hematologic: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia.

Allergic Reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. In addition, periarteritis nodosa and systemic lupus erythematosus have been reported.

Gastrointestinal: Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia.

Genitourinary: Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria and nephrotoxicity in association with cyclosporine.

Metabolic and Nutritional: Hyperkalemia, hyponatremia **(see PRECAUTIONS: Electrolyte Abnormalities).**

Neurologic: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache.

Psychiatric: Hallucinations, depression, apathy, nervousness.

Endocrine: The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Crosssensitivity may exist with these agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides.

Musculoskeletal: Arthralgia and myalgia. Isolated cases of rhabdomyolysis have been reported with sulfamethoxazole and trimethoprim, mainly in AIDS patients.

Respiratory: Cough, shortness of breath and pulmonary infiltrates (see WARNINGS).

Miscellaneous: Weakness, fatigue, insomnia.

POSTMARKETING EXPERIENCE The following adverse reactions have been identified during post-approval use of trimethoprim-sulfamethoxazole. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- Thrombotic thrombocytopenia purpura
- Idiopathic thrombocytopenic purpura
- QT prolongation resulting in ventricular tachycardia and *torsade de pointes*

OVERDOSAGE: *Acute*: The amount of a single dose of sulfamethoxazole and trimethoprim that is either associated with symptoms of overdosage or is likely to be life-threatening has not been reported. Signs and symptoms of overdosage reported with sulfonamides include anorexia, colic, nausea, vomiting, dizziness, headache, drowsiness and unconsciousness. Pyrexia, hematuria and crystalluria may be noted. Blood dyscrasias and jaundice are potential late manifestations of overdosage.

Signs of acute overdosage with trimethoprim include nausea, vomiting, dizziness, headache, mental depression, confusion and bone marrow depression.

General principles of treatment include the institution of gastric lavage or emesis, forcing oral fluids, and the administration of intravenous fluids if urine output is low and renal function is normal. Acidification of the urine will increase renal elimination of trimethoprim. The patient should be monitored with blood counts and appropriate blood chemistries, including electrolytes. If a significant blood dyscrasia or jaundice occurs, specific therapy should be instituted for these complications. Peritoneal dialysis is not effective and hemodialysis is only moderately effective in eliminating sulfamethoxazole and trimethoprim.

Chronic: Use of sulfamethoxazole and trimethoprim at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia and/or megaloblastic anemia. If signs of bone marrow depression occur, the patient should be given leucovorin 5 to 15 mg daily until normal hematopoiesis is restored.

DOSAGE AND ADMINISTRATION: Sulfamethoxazole and trimethoprim tablets are contraindicated in pediatric patients less than 2 months of age.

Urinary Tract Infections and Shigellosis in Adults and Pediatric Patients, and Acute Otitis Media in Children:

Adults: The usual adult dosage in the treatment of urinary tract infections is 1 sulfamethoxazole and trimethoprim DS (double strength) tablet or 2 sulfamethoxazole and trimethoprim tablets every 12 hours for 10 to 14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

Children: The recommended dose for children with urinary tract infections or acute otitis media is 40 mg/kg sulfamethoxazole and 8 mg/kg trimethoprim per 24 hours, given in two divided doses every 12 hours for 10 days. An identical daily dosage is used for 5 days in the treatment of shigellosis. The following table is a guideline for the attainment of this dosage:

Children 2 months of age or older:

Weight		Dose–every 12 hours
lb	kg	Tablets
22	10	–
44	20	1
66	30	1½
88	40	2 or 1 DS tablet

FOR PATIENTS WITH IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage should be employed using the following table:

Creatinine Clearance (mL/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15–30	½ the usual regimen
Below 15	Use not recommended

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS: The usual adult dosage in the treatment of acute exacerbations of chronic bronchitis is 1 sulfamethoxazole and trimethoprim DS (double strength) tablet or 2 sulfamethoxazole and trimethoprim tablets every 12 hours for 14 days.

PNEUMOCYSTIS JIROVECII PNEUMONIA:

Treatment: Adults and Children: The recommended dosage for treatment of patients with documented *Pneumocystis jirovecii* pneumonia is 75 to 100 mg/kg sulfamethoxazole and 15 to 20 mg/kg trimethoprim per 24 hours given in equally divided doses every 6 hours for 14 to 21 days.[9] The following table is a guideline for the upper limit of this dosage:

Weight		Dose–every 6 hours
lb	kg	Tablets
18	8	–
35	16	1
53	24	1½
70	32	2 or 1 DS tablet
88	40	2½
106	48	3 or 1½ DS tablets
141	64	4 or 2 DS tablets
176	80	5 or 2½ DS tablets

For the lower limit dose (75 mg/kg sulfamethoxazole and 15 mg/kg trimethoprim per 24 hours) administer 75% of the dose in the above table.

PROPHYLAXIS:
Adults: The recommended dosage for prophylaxis in adults is 1 sulfamethoxazole and trimethoprim DS (double strength) tablet daily.[10]

Children: For children, the recommended dose is 750 mg/m^2/day sulfamethoxazole with 150 mg/m^2/day trimethoprim given orally in equally divided doses twice a day, on 3 consecutive days per week. The total daily dose should not exceed 1600 mg sulfamethoxazole and 320 mg trimethoprim.[11] The following table is a guideline for the attainment of this dosage in children:

Body Surface Area	Dose– every 12 hours
(m^2)	Tablets
0.26	–
0.53	½
1.06	1

TRAVELER'S DIARRHEA IN ADULTS: For the treatment of traveler's diarrhea, the usual adult dosage is 1 sulfamethoxazole and trimethoprim DS (double strength) tablet or 2 sulfamethoxazole and trimethoprim tablets every 12 hours for 5 days.

HOW SUPPLIED: Sulfamethoxazole and Trimethoprim Tablets USP, 400 mg/80 mg are white to off-white circular, beveled edge uncoated tablets, debossed with "H 48" on one side and deep break line on the other side.

Bottles of 100 NDC 69043-010-01
Bottles of 500 NDC 69043-010-05

Sulfamethoxazole and Trimethoprim Tablets USP, 800 mg/160 mg are white to off-white oval, beveled edge uncoated tablets, debossed with "H 49" on one side and deep break line on other side.

Bottles of 100 NDC 69043-011-01
Bottles of 500 NDC 69043-011-05

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

REFERENCES:

1. Kremers P, Duvivier J, Heusghem C. Pharmacokinetic Studies of Co-Trimoxazole in Man after Single and Repeated Doses. *J Clin Pharmac*ol. Feb-Mar 1974; 14:112–117.
2. Kaplan SA, et al. Pharmacokinetic Profile of Trimethoprim-Sulfamethoxazole in Man. *J Infect Dis.* Nov 1973; 128 (Suppl): S547–S555.
3. Varoquaux O, et al. Pharmacokinetics of the trimethoprim-sulfamethoxazole combination in the elderly. *Br J Clin Pharmac*ol. 1985;20:575–581.
4. Safrin S, Lee BL, Sande MA. Adjunctive folinic acid with trimethoprimsulfamethoxazole for Pneumocystis carinii pneumonia in AIDS patients is associatedwith an increased risk of therapeutic failure and death. *J Infect Dis.* 1994 Oct;170(4):912-7.
5. Hardy DW, et al. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome. *N Engl J Med*. 1992; 327: 1842–1848.
6. Marinella Mark A. 1999. Trimethoprim-induced hyperkalemia: An analysis of reported cases. *Gerontol*. 45:209–212.
7. Margassery, S. and B. Bastani. 2002. Life threatening hyperkalemia and acidosis secondary to trimethoprim-sulfamethoxazole treatment. *J. Nephrol.* 14:410–414.
8. Brumfitt W, Pursell R. Trimethoprim/Sulfamethoxazole in the Treatment of Bacteriuria in Women. *J Infect Dis*. Nov 1973; 128 (Suppl):S657–S663.
9. Masur H. Prevention and treatment of Pneumocystis pneumonia. *N Engl J Med*. 1992; 327: 1853–1880.

10. Recommendations for prophylaxis against *Pneumocystis carinii* pneumonia for adults and adolescents infected with human immunodeficiency virus. *MMWR*. 1992; 41(RR-4):1–11.

11. CDC Guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for children infected with human immunodeficiency virus. *MMWR*. 1991; 40(RR-2):1–13.

Manufactured for:
Cronus Pharma LLC,
2 Tower Center Blvd, Suite - 1101A
East Brunswick, NJ 08816.
Contact No: 1-844-227-6687
(1-844-2-CRONUS)

Made in India
Code: TS/DRUGS/22/2009
Revised: 02/2021

Cronus Pharma

CRONUSPHARMAUSA.COM

2 Tower Center Blvd., Suite 1101A
East Brunswick, NJ 08816

1.844.227.6687
contact@cronuspharmausa.com

01.19.25