

TEPOXALIN Veterinary—Systemic[†]

A commonly used *brand name* for a veterinary-labeled product is *Zubrin*.

Note: For a listing of dosage forms and brand names by country availability, see the *Dosage Forms* section(s).

[†]Not commercially available in Canada.

Category: Analgesic; anti-inflammatory (nonsteroidal); antipyretic.

Indications

Accepted

Inflammation, musculoskeletal (treatment)¹; or
Pain, musculoskeletal (treatment)¹—*Dogs*: Tepoxalin is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.^{R-1}

¹Not included in Canadian product labeling or product not commercially available in Canada.

Regulatory Considerations

U.S.—

Tepoxalin is labeled only for use by or on the order of a licensed veterinarian.^{R-1}

Chemistry

Chemical name: 5-(4-chlorophenyl)-*N*-hydroxy-1-(4-methoxyphenyl)-*N*-methyl-1*H*-pyrazole-3-propanamide.^{R-1; 5}

Molecular formula: C₂₀H₂₀ClN₃O₃.^{R-1}

Molecular weight: 385.84.^{R-1}

Description: White, crystalline material with a melting range of 125 to 130 °C.^{R-1}

Solubility: Insoluble in water, soluble in alcohol and in most organic solvents.^{R-1}

Pharmacology/Pharmacokinetics

Note: The pharmacokinetic data for tepoxalin show large intrasubject and intersubject variability.^{R-1} An individual animal's metabolism and elimination of tepoxalin may vary significantly from the averages reported in this section.

Mechanism of action/Effect:

Anti-inflammatory—Tepoxalin is believed to act through the inhibition of cyclooxygenase activity and also the inhibition of lipoxygenase, making it a dual inhibitor of arachidonic acid metabolism.^{R-1} An *ex vivo* whole blood eicosanoid production assay following oral administration to dogs demonstrated the inhibition of prostaglandin F_{2α} and leukotriene B₄ by tepoxalin.^{R-6}

Other effects—Studies in laboratory animals have demonstrated less gastrointestinal ulcerogenic activity with tepoxalin administration than with some nonsteroidal anti-inflammatories, including diclofenac, indomethacin, or naproxen. The mechanism of action of this benefit is uncertain, although tissue-selective prostaglandin inhibition or a protective effect caused by 5-lipoxygenase inhibition have been suggested.^{R-6-8}

Absorption: Oral—*Dogs*: Tepoxalin is rapidly absorbed when administered orally.^{R-1} Tablets available in the United States are composed of micronized tepoxalin, which disintegrates quickly in the mouth.^{R-1}

Because tepoxalin is insoluble in water, it is more effectively absorbed when administered with food, especially meals high in fat, or within one to two hours of feeding.^{R-1}

Protein binding: *Dogs*—For tepoxalin and its acid metabolite: 98 to 99%.^{R-9}

Biotransformation: Tepoxalin is quickly converted to an active acid metabolite and other metabolites.^{R-1}

Half-life: Elimination—

Cats: With a single *oral* dose of 10 mg per kg of body weight—

Tepoxalin: 4.7 ± 0.8 hours.^{R-9}

Tepoxalin acid metabolite (active): 3.5 ± 0.4 hours.^{R-9}

Dogs: With an *oral* dose of 20 mg per kg of body weight (mg/kg) on the first day, followed by 10 mg/kg a day for 6 days—

Tepoxalin:

First day of treatment (reported as day 0): 2.0 ± 1.2 hours.^{R-1}

Second day (reported as day 1): 2.3 ± 1.4 hours.^{R-1}

Seventh day (reported as day 6): 1.6 ± 0.6 hours.^{R-1}

Tepoxalin acid metabolite (active):

First day of treatment (reported as day 0): 13.7 ± 10.7 hours.^{R-1}

Second day (reported as day 1): 12.4 ± 8.4 hours.^{R-1}

Seventh day (reported as day 6): 13.4 ± 10.3 hours.^{R-1}

Peak serum concentration:

Cats—With a single oral dose of 10 mg/kg:

Tepoxalin—2.3 ± 1.8 mcg/mL at 8.8 ± 4.3 hours.^{R-9}

Tepoxalin acid metabolite (active)—1.8 ± 1.2 mcg/mL at 7.8 ± 4.9 hours.^{R-9}

Dogs—With a single oral dose of 20 mg/kg on the first day, followed by 10 mg/kg a day for 6 days:

Tepoxalin—

First day of treatment (reported as day 0): 0.8 ± 0.5 mcg/mL at 2.3 ± 1.4 hours.^{R-1}

Second day (reported as day 1): 0.5 ± 0.2 mcg/mL at 2.3 ± 1.9 hours.^{R-1}

Seventh day (reported as day 6): 0.6 ± 0.3 mcg/mL at 2.8 ± 4.2 hours.^{R-1}

Tepoxalin acid metabolite (active)—

First day of treatment (reported as day 0): 0.8 ± 0.4 mcg/mL at 4.7 ± 6.2 hours.^{R-1}

Second day (reported as day 1): 1.0 ± 0.3 mcg/mL at 2.7 ± 1.9 hours.^{R-1}

Seventh day (reported as day 6): 1.0 ± 0.5 mcg/mL at 6.8 ± 8.0 hours.^{R-1}

Elimination: Tepoxalin is rapidly metabolized; the metabolites are eliminated almost entirely in the feces.^{R-1} The portion of the dose that is recovered in the urine (1%) is made up of metabolites that have not been identified.^{R-1}

Precautions to Consider

Reproduction/Pregnancy/Lactation

Dogs: The safety of administering tepoxalin to dogs during breeding, pregnancy, or lactation has not been studied.^{R-1}

Pediatrics

Dogs: The safety of administering tepoxalin to dogs younger than 6 months of age has not been studied.^{R-1}

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Anti-inflammatory drugs, nonsteroidal (NSAID) or
Corticosteroids

(concomitant administration of more than one NSAID or of corticosteroids concurrently with a NSAID, such as tepoxalin, may greatly increase the risk of adverse effects)^(R-1)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance).

Except under special circumstances, this medication should not be used when the following medical problems exist:

Cardiovascular disease^(R-1) or

Hepatic dysfunction^(R-1) or

Renal dysfunction^(R-1)

(because NSAIDs have been associated with renal toxicity in certain circumstances, risk to patients with cardiovascular, hepatic, or renal compromise may be increased; also, tepoxalin is metabolized by the liver)

Dehydration^(R-1)

(dehydration can increase the risk of renal toxicity)

Gastrointestinal ulceration

(many NSAIDs are known to increase the risk of gastrointestinal disease, particularly ulceration;^(R-1) therefore, the presence of pretreatment lesions may put an animal at risk of exacerbation or perforation)

Hypersensitivity to tepoxalin^(R-1)

(previous development of adverse effects from tepoxalin may be an indication of increased risk of future sensitivity)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; » = major clinical significance):

Blood chemistry, including serum bilirubin and

Complete blood count (CBC)

(periodic monitoring for anemia, icterus, or other evidence of adverse effects is recommended during treatment; in geriatric animals, pretreatment blood work may be advisable to rule out subclinical disease or establish baseline values)^(R-1)

Physical exam

(periodic physical exams and history updates are recommended during therapy to monitor efficacy and tolerance)^(R-1; 2)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

Note: As with other nonsteroidal anti-inflammatory drugs (NSAIDs), adverse effects, sometimes severe, may occur in individual animals with administration of tepoxalin.^(R-2) Gastrointestinal side effects are the most common;^(R-2) however, safety studies have shown evidence that tepoxalin can be tolerated by dogs, even with doses higher than the recommended dose (see also the *Overdose* section below in this monograph).

Because NSAIDs as a group are associated with adverse effects on hemostasis, renal function, and hepatic function, studies have been performed by the manufacturer to evaluate the effects of tepoxalin on these systems. When tepoxalin was administered in a randomized, blinded crossover study of ten healthy beagles at the recommended dose of 10 mg per kg of body weight (mg/kg) for seven days, no changes were seen in glomerular filtration rate as measured by renal scintigraphy.^(R-5)

Although tepoxalin is not labeled for preoperative administration, the following study results are provided as additional information about potential adverse effects. In a placebo-controlled study of twelve beagles, each dog was administered a single oral dose of tepoxalin, 10 mg/kg, two hours before undergoing surgery. The dogs were monitored for 48 hours after recovery from surgery. No significant changes were recorded in tests of hemostasis (hematology, platelet

count, buccal mucosal bleeding time, incisional bleeding), tests of renal function (serum blood urea nitrogen, serum creatinine, creatinine clearance, urine gamma-glutamyltransferase/creatinine ratio), or tests of hepatic function (serum alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase).^{R-5}

Those indicating need for medical attention

Reported during treatment with tepoxalin for 1 week:

Incidence less frequent

Dogs

Diarrhea (4% of dogs treated);^{R-1} **vomiting** (2%)^{R-1}

Incidence rare

Dogs

Incoordination (<1%)^{R-1}

Note: The effects listed above as reported during one week of therapy were observed in dogs undergoing a field study of tepoxalin versus a medication (carprofen) administered as an active control treatment.^{R-1; 3} Tepoxalin was administered at the labeled dose of 20 mg/kg on the first day, followed by 10 mg/kg a day for six days.^{R-1}

A nine-year-old dog died two days after completing the one-week study. Necropsy revealed gastric ulcerations, anemia, and severe diffuse gastroenteritis; however the death could not be definitely attributed to tepoxalin administration.^{R-1}

Reported during treatment with tepoxalin for 4 weeks:

Incidence more frequent

Dogs

Anorexia/inappetance (8% of dogs treated);^{R-1} **diarrhea** (22%);^{R-1} **vomiting** (20%)^{R-1}

Incidence less frequent

Dogs

Enteritis (4%);^{R-1} **lethargy** (3%)^{R-1}

Incidence rare

Dogs

Incontinence (<1%)^{R-1}

Note: The effects listed above as reported during 4 weeks of therapy were observed in a group of 107 dogs undergoing a field safety study without control animals. Dogs in this study were administered tepoxalin at the labeled dose of 20 mg/kg on the first day followed by 10 mg/kg a day for four weeks.^{R-1}

A twelve-year-old dog was found to have elevated liver enzymes and serum white cell count before entering the four-week study. Although tepoxalin treatment was discontinued after 14 days due to signs of drug intolerance (vomiting, diarrhea, inappetence, and gastrointestinal blood loss), dexamethasone was administered. The dog died the next day.^{R-1}

Those indicating need for medical attention only if they continue or are bothersome

Reported during treatment with tepoxalin for 4 weeks:

Incidence rare

Dogs

Appetite, increased (<1%);^{R-1} **eating grass** (<1%);^{R-1} **flatulence** (<1%);^{R-1} **hairloss** (<1%);^{R-1} **trembling** (<1%)^{R-1}

Overdose

For more information in cases of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the drug manufacturer.

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

Dogs

With a dose of 20 to 100 mg per kg of body weight (mg/kg) a day for 26 weeks, the following were reported during the treatment period.^{R-1}

Anemia; gastric irritation

Note: One of twenty-eight dogs treated in this dosage range (in the group of six receiving a dose of 20 mg/kg) was reported to have *anemia*, as demonstrated by decreased red blood cell count, serum hemoglobin, and packed cell volume. The anemia resolved during the study.

Gastric irritation (mucosal hemorrhage and congestion) was reported in one of six dogs in the placebo-treated group, in one of six receiving 20 mg/kg a day, in three of six dogs receiving 100 mg/kg a day, and in two of six receiving 300 mg/kg a day.

With a dose of 300 mg/kg a day for 26 weeks, the following were reported during the treatment period.^{R-1}

Gastric irritation or ulceration

Note: In this study, 3 out of 14 dogs that received the dose of 300 mg/kg a day developed *gastric ulceration*.^{R-1} Clinical pathology results reported for these dogs included decreases in red blood cell counts, serum hemoglobin, and packed cell volume; decreases in serum albumin, total protein, and calcium; and neutrophilic leukocytosis.^{R-1}

With a dose of 100 mg/kg a day for 52 weeks, the following were reported.^{R-1}

Gastric irritation or ulceration—ulceration was reported in 2 of 8 dogs treated

Client Consultation

A *Client Information Sheet* developed specifically for dog owners is provided by the United States manufacturer for clients administering oral tepoxalin to their dogs.^{R-1}

In providing consultation, consider emphasizing the following selected information:

Keeping water readily available during the treatment period to avoid dehydration

Never exceeding the prescribed daily amount without veterinary consultation; contacting a veterinarian if more than the daily dose is consumed^{R-2}

Familiarizing clients with signs that an adverse reaction may be occurring, including decrease or increase in appetite, vomiting, change in bowel movements, change in behavior, yellowing of gums, skin, or whites of the eyes, change in drinking habits, change in urination habits, or change in skin.^{R-2} Instructing them to discontinue medication and contact their veterinarian if a reaction is suspected

Not administering nonsteroidal anti-inflammatory drugs labeled for human use to animals without guidance from a veterinarian; human dosages may be toxic or fatal for animals

Veterinary Dosing Information

Oral administration

Because tepoxalin is insoluble in water, it is believed to be more effectively absorbed when administered with food, especially meals high in fat, or within one to two hours of feeding.^{R-1; 2}

When tepoxalin tablets are administered into a dog's mouth, it is recommended that the mouth be kept closed for approximately 4 seconds to ensure the tablet is dispersed.^{R-1}

The manufacturer states that dogs weighing less than 3 kg cannot be accurately dosed with tepoxalin tablets.^{R-1}

Oral Dosage Forms

TEPOXALIN TABLETS

Usual dose:

Inflammation, musculoskeletal¹; or

Pain, musculoskeletal¹—*Dogs*: Oral, 10 mg per kg of body weight every twenty-four hours.^{R-1} Alternatively, 20 mg per kg of body weight can be administered as an initial dose, followed by 10 mg per kg of body weight every twenty-four hours.^{R-1}

Note: If a rapid analgesic effect is necessary, for example, for dogs in severe osteoarthritic pain, it is recommended that the higher initial dose, 20 mg per kg of body weight (mg/kg) the first day, be administered to ensure that therapeutic concentrations are reached quickly.^{R-1}

Strength(s) usually available:

U.S.—^{R-1}

Veterinary-labeled product(s):

30 mg (Rx) [*Zubrin*].

50 mg (Rx) [*Zubrin*].

100 mg (Rx) [*Zubrin*].

200 mg (Rx) [*Zubrin*].

Canada—

Veterinary-labeled product(s):

Not commercially available.

Caution: Keep out of the reach of children.^{R-1}

Packaging and storage: Store between 2 and 30 °C (36 and 86 °F),^{R-1} unless otherwise specified by manufacturer.

USP requirements: Not in USP.^{R-4}

¹Not included in Canadian product labeling or product not commercially available in Canada.

Developed: 2/6/04

References

1. Zubrin package insert (Schering-Plough—US), Rev 2002, Rec 9/3/03.
2. Zubrin Client Information Sheet (Schering-Plough—US), Rev 2002. Available at www.zubrinus.com. Accessed on September 1, 2003.
3. Zubrin (tepopalin rapidly-disintegrating tablets) freedom of information summary (NADA # 141-193). Sponsor: Schering-Plough Animal Health. Approval Date: 3/31/03.
4. The United States pharmacopeia. The national formulary. USP 26th revision (January 1, 2003). NF 21st ed (January 1, 2003). Rockville, MD: The United States Pharmacopeial Convention, Inc., 2002.
5. Communication from Schering-Plough Animal Health on November 6, 2003. Unpublished data.
6. Argentieri DC, Ritchie DM, Ferro MP, et al. Tepoxalin: a dual cyclooxygenase/5-lipoxygenase inhibitor of arachidonic acid metabolism with potent anti-inflammatory activity and a favorable gastrointestinal profile. *J Pharmacol Exp Ther* 1994 Dec; 271(3): 1399-408.
7. Wallace JL, McCafferty DM, Carter L, et al. Tissue-selective inhibition of prostaglandin synthesis in rat by tepoxalin: anti-inflammatory without gastropathy? *Gastroenterology* 1993 Dec; 105(6): 1630-6.
8. Wallace JL, Cirino G, Cicala C, et al. Comparison of the ulcerogenic properties of tepoxalin with those of non-steroidal anti-inflammatory drugs (NSAIDs). *Agents Actions* 1991 Sep; 34(1-2): 247-50.
9. Committee comment, Rec 11/17/03 and 12/5/03.