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Veterinary Insights

Fever: Pathways and Antipyretic Mechanisms

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Introduction

Fever (pyrexia) is defined as "a state of elevated core temperature, which is often, but not necessarily part of the defensive response of multicellular organisms (hosts) to the invasion of live (microorganisms) or inanimate matter recognized as pathogenic or alien by the host."[1] Pyrexia is the body's endogenous response to infectious, inflammatory, and other processes which trigger the release of cytokines and pyrogens.[2] While pyrexia is something equine practitioners deal with on a weekly basis, when choosing if and how to control fever, it is worth taking a deeper look at how commonly used drugs affect the fever pathways.

Fever Pathways

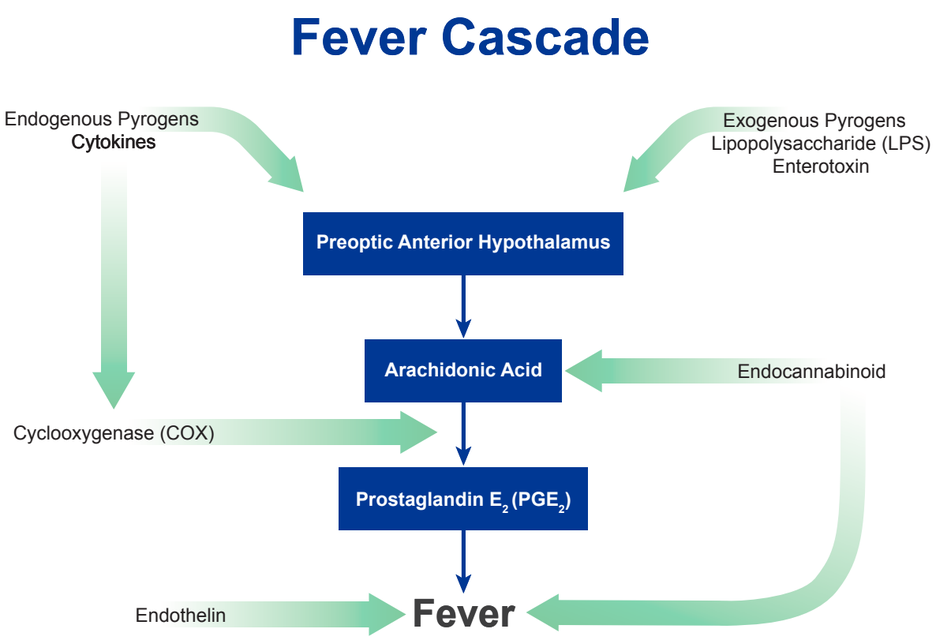
The most commonly understood pathway leading to fever involves cyclooxygenase (COX) and prostaglandins. Transported via the bloodstream, cytokines reach the preoptic-anterior hypothalamus (POAH), binding to specific receptors on neurons and endothelial cells in the area proximal to the organum vasculosum lamina terminalis (OVLT). Pyrogens – either endogenous or exogenous – activate and upregulate phospholipase A2, promoting the release of arachidonic acid. Additionally, the cytokines upregulate COX which catalyzes the conversion of arachidonic acid to prostaglandin E2 (PGE2). The PGE2 can then bind to E-type prostaglandin receptors, (EP-receptors), on the hypothalamus — specifically EP-3 receptors — resulting in the neuronal signaling leading to elevation of the hypothalamic set point. The elevation of the set point in the hypothalamic thermoregulatory center initiates a chain of events resulting in both behavioral and physiological responses generating and conserving body heat.[3,4] This is fever.

Newly Revealed Pathways

Two additional pathways have been uncovered relatively recently, within the last 25 years, that also contribute to the generation of fever. The endocannabinoid pathway provides a phospholipase-independent source of arachidonic acid for conversion to PGE2. This pathway involves hydrolysis of an endocannabinoid, 2-arachidonoylglycerol, catalyzed by monoacylglycerol lipase (MAGL) to produce arachidonic acid.[5,6]

Additional arachidonic acid may also be generated by degradation of the endocannabinoid anandamide [arachidonoylethanolamide (AEA)], catalyzed by fatty acid amide hydrolase (FAAH).[7] There is also evidence demonstrating a direct role of the central endocannabinoid system, via CB1 receptors, mediating fevers induced by the exogenous pyrogen LPS.[8] This is a non-prostaglandin dependent pathway.

There is also another prostaglandin independent fever pathway via the central nervous system endothelin system. Research has demonstrated that fever induced by lipopolysaccharide (LPS) from gram negative bacteria can result from release of endothelin 1 (ET-1) in the central nervous system, without an increase in prostaglandin levels, and which is not inhibited by a classic nonsteroidal anti-inflammatory drug (NSAID), indomethacin.[9,10]



NSAIDs Class

The nonsteroidal anti-inflammatory drugs are grouped together as a functional classification of drugs based on their clinical profile. The NSAIDs are known for a range of clinical effects including varying degrees of anti-inflammatory, anti-pyretic, and analgesic effects,[11] but not all NSAIDs have been studied or FDA-approved for all of the effects. Inhibition of COX is the shared characteristic among NSAIDs; however, other receptor interactions may play a role in the clinical effects of some drugs within this class and some NSAIDs have demonstrated antipyretic effects unrelated to COX inhibition.[10] NSAIDs differ in their chemical structure and classification but maintain similarity in their clinical behavior.[12]

As a class, NSAIDs may be associated with platelet dysfunction, coagulopathy, gastrointestinal toxicity, and renal toxicity.[13-15] Sensitivity to drug associated adverse effects varies with the individual patient.[13-15] Consider stopping therapy if adverse reactions, such as prolonged inappetence or abnormal feces occur which could be attributed to gastrointestinal toxicity.[13,15] Patients at greatest risk for adverse events are those that are dehydrated, on diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction.[13-15] Concurrent administration of potentially nephrotoxic drugs should be carefully approached or avoided.[13,15] Since many NSAIDs possess the potential to induce gastrointestinal ulceration, concomitant use of any NSAID with other anti-inflammatory drugs, such as other NSAIDs and corticosteroids, should be avoided.[13-15] Risk of adverse events may be greater in dehydrated patients or those with existing renal dysfunction, or in patients with pre-existing gastrointestinal ulcerative disease.

COX Isoenzymes

Since all NSAIDs inhibit COX, they may also be classified according to their selectivity for COX isoenzyme inhibition. COX has at least three isoenzymes. COX-1 is constitutively expressed in most tissues and is responsible for production of eicosanoids (including prostaglandins and thromboxane) from arachidonic acid that maintain normal physiologic functions of organ systems, including renal blood flow and the mucosal lining of the gastrointestinal tract.[16] COX-2 is inducible and believed to be responsible for the pain and inflammation associated with cyclooxygenase activity.[16] COX-3, a variant of COX-1, is mainly expressed in the central nervous system and believed to be associated with pain and pyrexia.[16,17] (See Table 1.) The classic NSAIDs inhibit both COX-1 and COX-2 isoenzymes, and the coxibs selectively inhibit COX-2. Within the NSAID class there is variability amongst the drugs in the relative inhibition of COX isoenzymes. The NSAIDs FDA-approved for use in horses — phenylbutazone, flunixin meglumine, dipyrone, firocoxib, and ketoprofen — all inhibit both COX-1 and COX-2 isoenzymes — albeit with varying potency. Firocoxib is a selective COX-2 inhibitor. Although the clinical relevance of receptor interactions in the horse has not been completely elucidated, dipyrone has been shown in vitro to be a potent inhibitor of COX-3.[17] Dipyrone has demonstrated more potent inhibition of COX-3 than either COX-1 or COX-2, which may account for its relatively weak peripheral effects.[17,18]

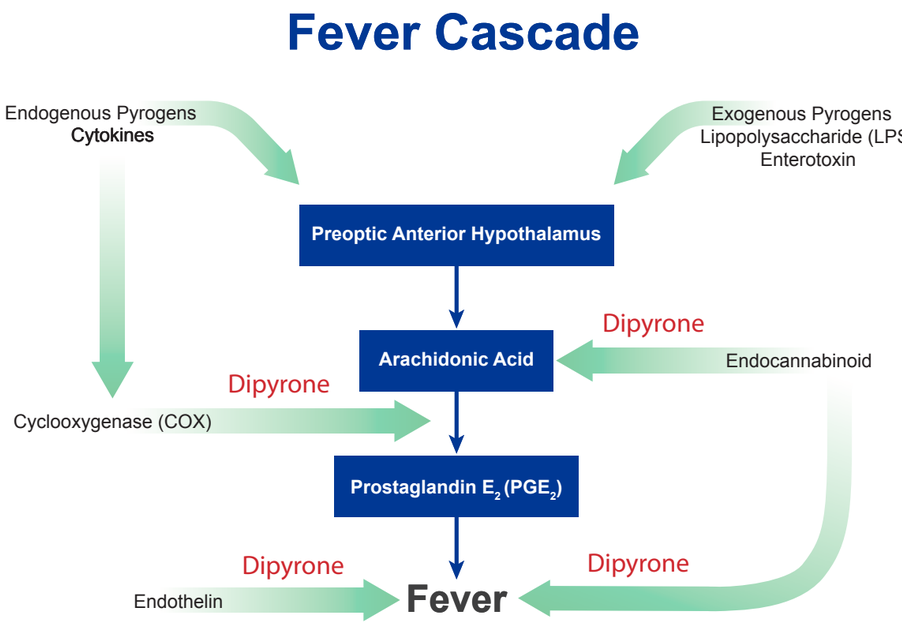
Table 1[16,17]

COX Isoenzyme	Characteristic	Distribution	Major Functions
COX-1	Constitutive	Most tissues	Homeostasis, maintains normal physiological functions
COX-2	Inducible	Most tissues	Inflammation, pain
COX-3	Variant of COX-1	Mainly central nervous system	Fever, pain

Cyclooxygenase has two enzymatic activities, a cyclooxygenase activity and a peroxidase activity.[19] The classic NSAIDs inhibit COX activity by competing with arachidonic acid and reversibly binding to the cyclooxygenase active site.[19] In contrast to classic NSAIDs, dipyrone does not compete for the cyclooxygenase site on COX, but reversibly inhibits the enzyme by reducing the higher oxidation states of COX and/or sequestering peroxides, similar to the mechanism of action of paracetamol (acetaminophen).[19]

Dipyrone Mechanism of Action as an Antipyretic

The antipyretic effect of dipyrone has been demonstrated to be the result of central COX inhibition and decreased production of prostaglandin E2 (PGE2).[17] In addition to the COX and prostaglandin dependent mechanism of antipyresis, dipyrone has demonstrated a non-COX related and non-prostaglandin dependent antipyretic effect mediated by the central endothelin system.[10] In this study the same effect was not demonstrated by a classic NSAID (indomethacin), leading the investigators to suggest that dipyrone has a distinct profile of antipyretic action from other COX inhibitors.[10] Dipyrone has demonstrated interactions with the central endocannabinoid system,[20] and may inhibit further production of arachidonic acid that can be converted into pyrexia producing PGE2. Dipyrone may also be postulated to act as an antipyretic via interactions with the endocannabinoid system and the direct, non-arachidonic acid and non-prostaglandin dependent pathway demonstrated with LPS induced fevers.[8] The clinical relevance of these postulated mechanisms of action as an antipyretic have not been determined in the horse.



Summary

Dipyrone is a member of the NSAID class. NSAIDs are known for a range of clinical effects including varying degrees of anti-inflammatory, anti-pyretic, and analgesic effects, but not all NSAIDs have been studied or FDA-approved for all of the effects. All members of the class share inhibition of COX as a mechanism of action. However, dipyrone differs from other NSAIDs with regard to the binding site on COX that is inhibited and has demonstrated more potent inhibition of COX-3 than COX-1 or COX-2. Through interactions with the endocannabinoid system, dipyrone may decrease arachidonic acid levels that can be converted into PGE2.

Dipyrone has also shown additional antipyretic effects unrelated to COX inhibition. Both the endothelin system and a non-arachidonic acid non-prostaglandin dependent endocannabinoid system pathway to fever have been demonstrated. Dipyrone has shown antipyretic effects via the endothelin system and may be postulated to act as an antipyretic via displayed interactions with the endocannabinoid system. As an antipyretic, dipyrone has demonstrated a multi-modal mechanism of action.*

**Clinical relevance is unknown.*

Zimeta is indicated for the control of pyrexia in horses.

Important Safety Information

Zimeta® (dipyrone injection) should not be used more frequently than every 12 hours. For use in horses only. Do not use in horses with a hypersensitivity to dipyrone, horses intended for human consumption or any food producing animals, including lactating dairy animals. Not for use in humans, avoid contact with skin and keep out of reach of children. Take care to avoid accidental self-injection and use routine precautions when handling and using loaded syringes. Prior to use, horses should undergo a thorough history and physical examination. Monitor for clinical signs of coagulopathy and use caution in horses at risk for hemorrhage. Concomitant use with other NSAIDs, corticosteroids and nephrotoxic drugs, should be avoided. As a class, NSAIDs may be associated with gastrointestinal, renal, and hepatic toxicity. The most common adverse reactions observed during clinical trials were Elevated Serum Sorbitol Dehydrogenase (SDH), Hypoalbuminemia and Gastric Ulcers. **For product label, including complete safety information, see enclosed product insert or visit Zimeta.com/PI.**

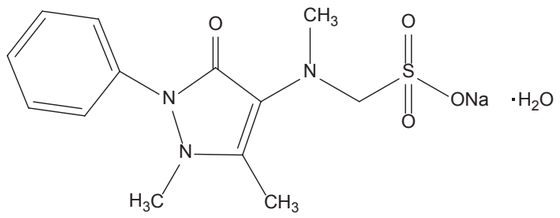
Zimeta®
(dipyrone injection)

500 mg/mL injection
For intravenous use in horses
Non-steroidal anti-inflammatory drug (NSAID)

CAUTION: Federal law (U.S.A.) restricts this drug to use by or on the order of a licensed veterinarian.

Description: Dipyrone belongs to the pyrazolone class of non-steroidal anti-inflammatory (NSAID) drugs. Chemically, dipyrone is metamizole sodium. Each mL of this clear sterile solution for intravenous injection contains 500 mg dipyrone and 10 mg benzyl alcohol in water.

The structural formula of dipyrone is:



Molecular Formula: $C_{13}H_{16}N_3NaO_4S \bullet H_20$ Molecular Weight: 351.4

Indication: Zimeta® (dipyroine injection) is indicated for the control of pyrexia in horses.

Dosage and Administration: Always provide the Client Information Sheet with the prescription. Administer Zimeta by intravenous injection, once or twice daily, at 12 hour intervals, for up to three days, at a dosage of 30 mg/kg (13.6 mg/lb). The overall number of doses and duration of treatment with Zimeta is dependent on the response observed (fever reduction). Zimeta may be re-administered based on recurrence of fever for up to 3 days. Zimeta is provided in a multi-dose vial and contains a preservative.

Contraindications: Horses with hypersensitivity to dipyrone should not receive Zimeta. Due to the prolongation of prothrombin time (PT) and associated clinical signs of coagulopathy, dipyrone should not be given more frequently than every 12 hours.

Warnings: For use in horses only. Do not use in horses intended for human consumption. Do not use in any food producing animals, including lactating dairy animals.

Human Warnings: Care should be taken to ensure that dipyrone is not accidentally injected into humans as studies have indicated that dipyrone can cause agranulocytosis in humans.

Not for use in humans. Keep this and all drugs out of reach of children. In case of accidental exposure, contact a physician immediately. Direct contact with the skin should be avoided. If contact occurs, the skin should be washed immediately with soap and water. 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: Horses should undergo a thorough history and physical examination before initiation of any NSAID therapy.

As a class, NSAIDs may be associated with platelet dysfunction and coagulopathy. Zimeta has been shown to cause prolongation of coagulation parameters in horses. Therefore, horses on Zimeta should be monitored for clinical signs of coagulopathy. Caution should be used in horses at risk for hemorrhage.

As a class, NSAIDs may be associated with gastrointestinal, renal, and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Consider stopping therapy if adverse reactions, such as prolonged inappetence or abnormal feces, could be attributed to gastrointestinal toxicity.

Patients at greatest risk for adverse events are those that are dehydrated, on diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached or avoided. Since many NSAIDs possess the potential to produce gastrointestinal ulcerations and/or gastrointestinal perforation, concomitant use of Zimeta with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. The influence of concomitant drugs that may inhibit the metabolism of Zimeta has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

The safe use of Zimeta in horses less than three years of age, horses used for breeding, or in pregnant or lactating mares has not been evaluated. Consider appropriate washout times when switching from one NSAID to another NSAID or a corticosteroid.

Adverse Reactions: Adverse reactions reported in a controlled field study of 138 horses of various breeds, ranging in age from 1 to 32 years of age, treated with Zimeta (n=107) or control product (n=31) are summarized in Table 1. The control product was a vehicle control (solution minus dipyrone) with additional ingredients added to maintain masking during administration.

Horses may have experienced more than one of the observed adverse reactions during the field study. Horses may have received one or more doses of Zimeta during the field study. The control product was only administered once.

Table 1: Adverse Reactions Reported During the Field Study with Zimeta

Adverse Reaction	Zimeta® (dipyrone injection) (N=107)	Control Product (N=31)
Elevated Serum Sorbitol Dehydrogenase (SDH)	5 (5%)	5 (16%)
Hypoalbuminemia	3 (3%)	1 (3%)
Gastric Ulcers	2 (2%)	0 (0%)
Hyperemic Mucosa Right Dorsal Colon	1 (1%)	0 (0%)
Prolonged Activated Partial Thromboplastin Time (APTT)	1 (1%)	0 (0%)
Elevated Creatinine	1 (1%)	0 (0%)
Injection Site Reaction	1 (1%)	0 (0%)
Anorexia	1 (1%)	1 (3%)

Horses with elevated SDH, hypoalbuminemia, prolonged APTT, or elevated creatinine did not show associated clinical signs. One horse exhibited an exacerbation of pre-existing hypoalbuminemia after treatment; this horse also showed concurrent elevation in SDH. Two horses that received Zimeta were diagnosed with gastric ulcers. One horse that received 4 doses of Zimeta was diagnosed with grade III/IV gastric ulceration and hyperemia of the mucosa of the right dorsal colon on post-mortem examination which was performed following euthanasia due to illness unrelated to treatment (septic arthritis and cellulitis). This horse was previously treated with a different NSAID prior to enrollment in the study. A second horse that enrolled in the study due to a mandibular facial wound, and received two doses of Zimeta, was diagnosed with grade III/IV gastric ulcers 4 days following completion of the field study.

In the field study, Zimeta was used concomitantly with other therapies, including antibiotics and sedatives.

Information for Owners or Person Treating Horse: A Client Information Sheet should be provided to the person treating the horse. Treatment administrators and caretakers should be aware of the potential for adverse reactions and the clinical signs associated with NSAID intolerance. Adverse reactions may include colic, diarrhea, and decreased appetite. Serious adverse reactions can occur without warning and, in some situations, result in death. Clients should be advised to discontinue NSAID therapy and contact their veterinarian immediately if any signs of intolerance are observed.

Clinical Pharmacology: Dipyrone is a water soluble pyrazolone derivative that functions as a pro-drug and is immediately hydrolyzed to 4-methlyaminoantipyrine (4-MAA) following administration by any route.[1] In most species, including the horse, 4-MAA is the molecule assayed for pharmacokinetics, as dipyrone is present for an extremely short period of time.[2] In humans, 4-MAA is further metabolized by the liver to secondary metabolites that primarily undergo renal excretion. 4-MAA is also the molecule associated with clinical efficacy in humans. The mechanism of action to reduce pyrexia has not been fully characterized.

The mean (± SD) 4-MAA pharmacokinetic parameters after a single intravenous dose of 30 mg/kg dipyrone administered every 12 hours for 9 days to 6 adult horses were as follows: maximum concentration (C_{max}) of 40,616.67 (9,917.34) ng/mL, area under the concentration vs time curve for the dosing interval (AUC_{tau}) of 106,848.75 (12,128.88) hr*ng/mL, volume of distribution (V_z) of 1,607.43 (165.51) mL/kg, clearance at steady state (CL_{ss}) of 284.17 (36.08) mL/kg/hr, and half-life of 3.94 (0.44) hours.

Effectiveness: One hundred and thirty-eight (138) horses were enrolled in a field effectiveness study. The field study was divided into two phases; an effectiveness phase and an extended use field safety phase.

The effectiveness phase was a randomized, masked, controlled, multicenter, field study conducted to evaluate the effectiveness of Zimeta® (dipyrone injection) administered intravenously at 30 mg/kg bodyweight in horses over one year of age with naturally occurring fevers. Enrolled horses had a rectal temperature ≥102.0°F. A horse was considered a treatment success if 6 hours following a single dose of study drug administration the rectal temperature decreased ≥2.0°F from hour 0, or the temperature decreased to normal (≤101.0°F).

One hundred and thirty-eight horses received treatment (104 Zimeta and 34 control product) and 137 horses (103 Zimeta and 34 control product) were included in the statistical analysis for effectiveness. At 6 hours post-treatment, the success rate was 74.8% (77/103) of Zimeta treated horses and 20.6% (7/34) of control horses. The results of the field study demonstrate that Zimeta administered at 30 mg/kg intravenously was effective for the control of pyrexia 6 hours following treatment administration.

The extended use field safety phase was an open-label field study to evaluate the safety of Zimeta when administered intravenously at 30 mg/kg bodyweight to horses with pyrexia under field conditions. Eighty-seven horses from the first phase entered this phase. During the extended use field safety phase, horses may have received more than one dose of Zimeta. Most horses in the study were treated with Zimeta once per day. No horses were treated with Zimeta more than twice daily.

Animal Safety: A pilot laboratory study was conducted in 31 adult horses, ages 3 years to 20 years, with naturally occurring fever (due to respiratory disease or other infectious process) to evaluate the effectiveness of a non-final market formulation of dipyrone injection at a dose of 30 mg/kg intravenously. One horse developed soft feces after treatment with one dose of dipyrone injection and a second horse developed bloody nasal discharge and died one day after receiving one dose of dipyrone injection. Necropsy findings for the horse that died documented severe pleuropneumonia; however, due to the potential effects of dipyrone on platelet aggregation and function, the occurrence of bloody nasal discharge and progression of disease in this horse may be related to treatment. There were no substantive differences between the non-final market formulation used in this pilot study and Zimeta.

A laboratory safety study was conducted in which Zimeta was administered via intravenous catheter to 32 healthy adult horses at 0, 30, 60, and 90 mg/kg (0, 1, 2, and 3X the recommended dose) three times a day (TID), every 8 hours, for 9 consecutive days. Horses in the control group were administered placebo (saline).

The most common post-treatment observations were cough, depression, tachypnea or dyspnea, epistaxis, nasal discharge, inappetence, loose manure, colic and fever. Many of these clinical signs were associated with infectious respiratory disease, which affected horses in all treatment groups. One horse in the 3X group died. This horse had pleuropneumonia and observations of epistaxis for 46 hours with increasing dyspnea prior to spontaneous death, and associated prolongations in both prothrombin time (PT) and activated partial thromboplastin time (APTT). Another horse in the 3X group had nasal discharge with epistaxis that resolved prior to study completion, with associated prolongations in both PT and APTT on Day 8. This horse also had clinical signs and necropsy findings consistent with pneumonia and coagulopathy including: hemorrhage from previous catheter site, renal abscessation with hemorrhage, and petechial and ecchymotic hemorrhage of the ileum. Overall, PT was statistically significantly prolonged for the horses in the 2X and 3X dose groups when compared to control horses (p=0.0037).

Other treatment-related effects included an increase in liver weight and an elevation in total bilirubin. These findings were not associated with clinical signs or liver pathology. On necropsy, duodenal erosion was present in one 3X TID horse. Stomach (non-glandular) erosions were present in one control horse and two 1X TID horses. Stomach (non-glandular) ulcers were present in one control horse and one 2X TID horse. No erosions or ulcerations were identified in the large intestine. On histopathology, there were three 1X TID horses, two 2X TID horses, and three 3X TID horses with minimal or mild renal tubular dilation. One 1X TID horse and two 3X TID horses had minimal renal tubular mineralization. These histopathology changes were not associated with changes on gross necropsy, in clinical pathology or clinical signs of renal dysfunction.

Due to the prolongation of PT and associated clinical signs of coagulopathy, this study did not demonstrate an adequate margin of safety when Zimeta was administered IV three times daily (every 8 hours).

To further evaluate the effects of Zimeta on coagulation, an additional laboratory study was conducted. Zimeta was administered via intravenous catheter to 32 healthy adult horses at 0, 30, 60, and 90 mg/kg (0, 1, 2, and 3X the recommended dose) every 12 hours (BID) for 9 consecutive days, and at 30 and 60 mg/kg (1X and 2X the recommended dose) TID for 9 consecutive days. Horses in the control group were administered placebo (saline). The most common treatment-related adverse effects were anorexia, depression, and loose feces. Seven horses in Zimeta treatment groups experienced one or more of these adverse effects, as compared to no horses in the control group. One horse in the 2X TID group had varying degrees of depression, loose feces and colic for multiple days during the study, which resolved with hand walking.

At the completion of the study, horses were healthy when returned to the source herd. There was an upward numerical trend in the PT which suggested a treatment effect of dipyrone injection on prolongation of PT; however, the overall treatment effect was not significant (p=0.1131). There was no evidence of clinical signs related to coagulopathy. This study supported the conclusion that there is an adequate margin of safety when Zimeta is administered at 30 mg/kg IV twice daily (every 12 hours) for three days.

For pharmacokinetic results see summary in Clinical Pharmacology section.

Storage Information: Store at Controlled Room Temperature between 20° and 25°C (68° and 77°F); with excursions permitted between 15° and 30°C (59° and 86°F). Protect from light. Multi-dose vial. Use within 30 days of first puncture.

How Supplied: Zimeta is available as a 500 mg/mL solution in a 100 mL, multi-dose vial.

Approved by FDA under NADA # 141-513
NDC 17033-905-10

Manufactured for:
Dechra Veterinary Products
7015 College Blvd, Suite 525
Overland Park, KS 66211 USA

For a copy of the Safety Data Sheet (SDS) or to report adverse reactions call Dechra Veterinary Products at 1-866-933-2472.

Rev. December 2020

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