

Zimeta[®]

(dipyrone injection)



Relieve pyrexia at the source with Zimeta[®]

The first and only drug FDA-approved for control of pyrexia in horses¹



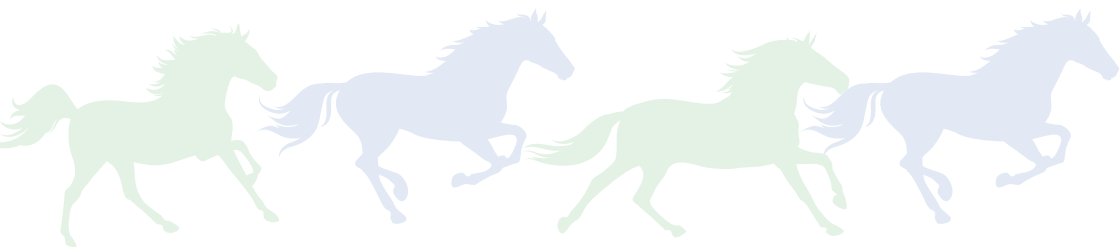
Important Safety Information

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.**

Rapid and effective fever control^{1,2*}

In a clinical study, Zimeta significantly reduced fever in horses with naturally occurring disease, including respiratory disease, when checked 6 hours post-dosing²

In a study, Zimeta reduced fever $\geq 2.0^{\circ}\text{F}$, or the temperature decreased to normal ($\leq 101.0^{\circ}\text{F}$), in 74.8% of treated horses compared to 20.6% in the placebo group when checked at 6 hours.¹



**When administered according to label directions*

Important Safety Information

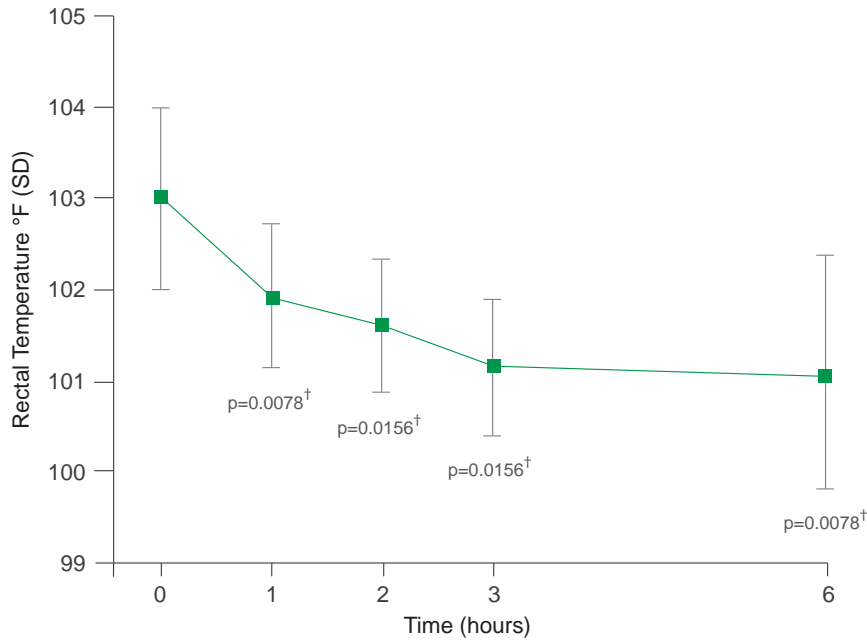
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Zimeta[®]
(dipyron injection)


“In my experience dipyron works quickly against fever, and that’s important to me as a practitioner and to the horses in my practice. In my mind, it’s a more specific medication for fever. You’re not going to use a hammer to punch in something that needs a finger. I like the specificity of it and the safety of it.”

– Carol Clark, DVM, Dipl., ACVIM

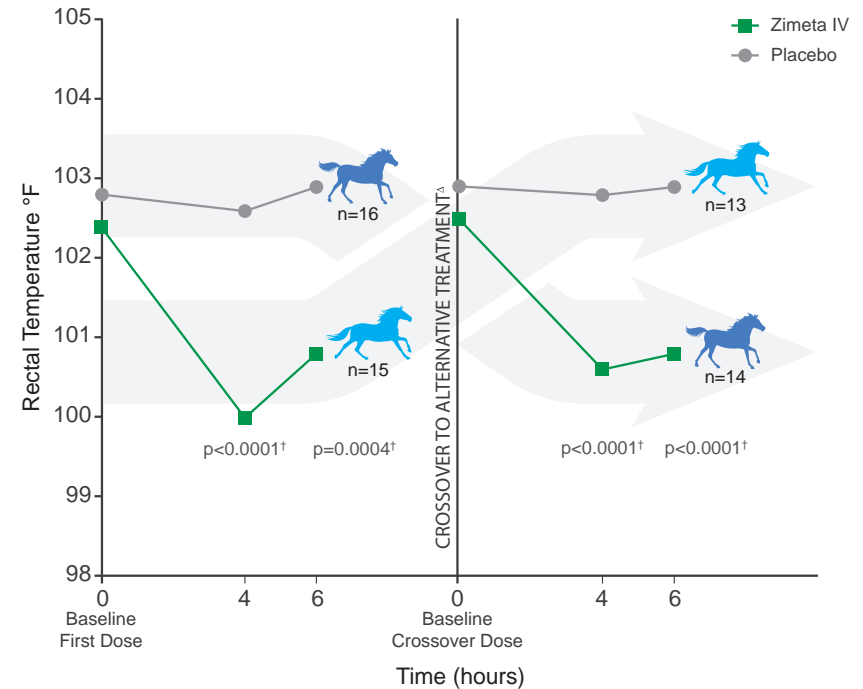
RAPID REDUCTION OF FEVER FOLLOWING A SINGLE DOSE OF ZIMETA IV³



[†]Wilcoxon signed rank test compared to baseline
N=8
SD = standard deviation

In a clinical pilot study of eight horses, Zimeta significantly reduced fever in horses with naturally occurring disease following one dose of Zimeta.³

TEMPERATURE REDUCTION WITH ZIMETA IV (CROSSOVER STUDY)⁴



[^]Crossover baseline was 24-30 hours after the first dose
[†]Wilcoxon signed rank test compared to baseline

In a clinical crossover study, horses with naturally occurring fever were administered either Zimeta or a placebo. Twenty-four hours after the initial dose, qualifying (febrile) horses received the opposite treatment. During both phases of the study, **only Zimeta-treated horses demonstrated statistically significant reduction in fever.**⁴

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.**

Proven safety profile

Zimeta was proven safe when administered once or twice daily at 12-hour intervals for up to 3 days^{1*}

- In a study, clinical signs associated with adverse events were reported in $\leq 2\%$ of Zimeta treated horses.¹
- Dipyron, the active ingredient in Zimeta, has been shown to have low peripheral cyclo-oxygenase (COX) inhibitory activity.^{5**}
- The effect of Zimeta on the gastrointestinal system has not been specifically studied. While horses in the studies did not show clinical signs generally associated with gastrointestinal ulceration, researchers did not specifically examine for ulcers before or after treatment with Zimeta.^{2,6†}
- In the field study, Zimeta was used concomitantly with other therapies, including antibiotics and sedatives.¹

**When administered according to label directions*

***Equine clinical relevance has not been determined*

†Two horses (out of 107) in the field study were diagnosed with gastric ulcers after the study concluded. Neither of these horses had gastroscopy performed prior to inclusion in the study, thus the correlation between treatment and ulcer formation is not known.^{1,2,6}

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“Dipyron was always my first choice for fever because of its rapid onset. It was a good choice because controlling the fever quickly helped to get the horse back to eating and drinking. Using dipyron, I had a sense of where I was with my patient. If I’m masking a fever from pleuritis or pneumonia, I may not know if I’m using the right antibiotic.”

– Richard D. Mitchell, DVM, MRCVS, Dipl. ACVSMR

Centrally acting fever reduction

Dipyrone's mechanism of action is focused in the central nervous system where fever is regulated**

Use guidance in competitive horses

- Horses competing under United States Equestrian Federation (USEF) and American Quarter Horse Association (AQHA) rules can be administered Zimeta with a medication report form documenting a 24-hour withdrawal. The administration of Zimeta does not constitute the use of a second NSAID, which is prohibited by USEF and AQHA rules.^{7,8} Users should consult governing bodies of other organizations for more details.
- Of the non-steroidal anti-inflammatory drugs approved in the United States listed by the Fédération Equestre Internationale (FEI), dipyrone has the shortest established detection time in horses at 72 hours.⁹

***Equine clinical relevance has not been determined*

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.**



Zimeta is a clear (not cloudy), light yellow to yellow solution.

Dosing and administration

- Zimeta is provided as a 500 mg/mL injection in a 100 mL, multi-dose vial¹
- Administer Zimeta intravenously at 30 mg/kg every 12 hours as needed for up to three days¹
- Zimeta does not require refrigeration

Zimeta[®]

(dipyrone injection)

500 mg/mL injection

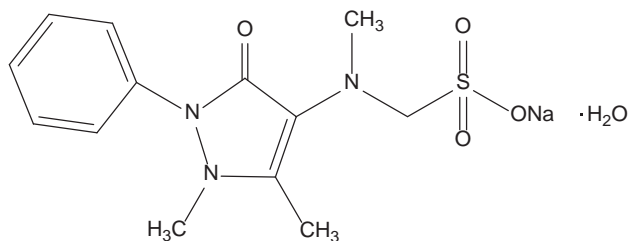
For intravenous use in horses

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: C₁₃H₁₆N₃NaO₄S • H₂O Molecular Weight: 351.4

Indication: Zimeta[®] (dipyrone 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-methylaminoantipyrine (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_{0-24}) of 106,848.75 (12,128.88) hr*ng/mL, volume of distribution (V_d) 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® (dipyron 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 $\geq 102.0^\circ\text{F}$. A horse was considered a treatment success if 6 hours following a single dose of study drug administration the rectal temperature decreased $\geq 2.0^\circ\text{F}$ from hour 0, or the temperature decreased to normal ($\leq 101.0^\circ\text{F}$).

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 dipyron injection at a dose of 30 mg/kg intravenously. One horse developed soft feces after treatment with one dose of dipyron injection and a second horse developed bloody nasal discharge and died one day after receiving one dose of dipyron injection. Necropsy findings for the horse that died documented severe pleuropneumonia; however, due to the potential effects of dipyron 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 dipyron 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.

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Rev. December 2020

¹Levy M, Zylber-Katz E, Rosenkranz B. Clinical Pharmacokinetics of Dipyron and its Metabolites. Clin Pharmacokinet. 1995; 28(3):216-231.

²Metamizole Summary Report. Committee for Veterinary Medicinal Products: The European Agency for the Evaluation of Medicinal Products. June 2003. EMA/MRL/878/03-Final



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For more information, contact your Dechra Representative or call (866) 683-0660, your preferred animal health distributor, or visit Zimeta.com.

For 24-hour Veterinary Technical Support, contact Dechra Veterinary Products at:
866-933-2472 | www.dechra-us.com | support@dechra.com

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References: **1.** Zimeta® (dipyrone injection) [package insert], Rev. 12/2020. **2.** Morrese PR, White GW, Poole HM, et al. Randomized blinded controlled trial of dipyrone as a treatment for pyrexia in horses. *Am J Vet Res.* 2019;80(3):294-299. **3.** Data on file. REF-0167. Dechra Ltd. **4.** Data on file. REF-0269. Dechra Ltd. **5.** Rogosch T, Sinning C, Podlewski A, et al. Novel bioactive metabolites of dipyrone (metamizol). *Bioorg Med Chem.* 2012;20(1):101-107. **6.** Data on file. REF-0283. Dechra Ltd. **7.** United States Equestrian Federation. US Equestrian Announces Requirements for Use of FDA-Approved Zimeta™ (Dipyrone Injection). Dec. 31, 2019. Available at: <https://www.usef.org/media/press-releases/us-equestrian-announces-requirements-for-use-of>. [Access Date: Jan. 12, 2021]. **8.** American Quarter Horse Association. Zimeta Approved by AQHA as a Therapeutic Medication. January 28, 2020. Available at: <https://www.aqha.com/-/zimeta-approved-by-aqha-as-a-therapeutic-medication>. [Access Date: Jan. 12, 2021]. **9.** Fédération Equestre Internationale. FEI List of Detection Times. July 13, 2018. Available from: https://inside.fei.org/system/files/FEI%20Detection%20Times%202018_0.pdf. [Access Date: Jan. 12, 2021].