Horses should undergo a thorough history and physical examination before initiation of any NSAID therapy.

As a drug, NOAls 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 drug, NOAls 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 ileus 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. Continued administration of potentially nephrotoxic drugs should be carefully approached or avoided. Since many NOAls possess the potential to produce gastrointestinal ulcerations and/or gastrointestinal perforation, concomitant use of Zimeta with other anti-inflammatory drugs, such as NOAls 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 withholding times when switching from one NOAl to another NOAl 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 12 years of age, treated with Zimeta (n=107) or control product (n=31) are summarized in Table 1. The control product was a veterinary control solution minus dipyrone. Additional ingredients added to maintain masking during administration.

Horses may have experienced more than one of the observed adverse drug 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 one.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Zimeta™ (dipyrone injection)</th>
<th>Control Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td>(n=107)</td>
<td>(n=31)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2 (2%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Proton Pump Inhibitor</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Proctitis</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Injection Site Reaction</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Adverse reactions associated with the control product were as follows: maximum concentration (Cmax) of 40,616.67 (9,917.34) mg/L, area under the curve (AUC) of 104,616.7 (9.173.4) mg*hr/mL, and area under the curve vs time for the dosing interval.

Zimeta™ (dipyrone injection)

Non-steroidal anti-inflammatory drug for intravenous use in horses only.

INFORMATION FOR HORSE OWNERS:

Indication: Zimeta™ (dipyrone injection) is administered once or twice daily for up to 3 days to control fever in horses. The overall duration of treatment with Zimeta (dipyrone injection) will be dependent on the response observed (fever reduction), but should not exceed 3 days. Zimeta should not be administered more frequently than every 12 hours.

This summary contains important information about Zimeta. You should read the information before Zimeta is administered to your horse. This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you do not understand any of this information or you want to know more about Zimeta.

WHAT IS ZIMETA™?

Zimeta is a non-steroidal, non-anti-inflammatory drug (NOAl) of the pyrazolone class used to control fever in horses by veterinary prescription only. Fever is an elevation in body temperature due to a variety of infectious and inflammatory conditions in the horse.

HOW TO GIVE ZIMETA TO YOUR HORSE

Zimeta should be given according to your veterinarian’s instructions. Do not change the way you give Zimeta to your horse without first speaking with your veterinarian.

WHAT KIND OF RESULTS CAN I EXPECT WHEN MY HORSE IS BEING TREATED WITH ZIMETA FOR A FEVER?

Zimeta is an anti-inflammatory drug that can control fever that is a result of infection or inflammation; however, this is just one of the many functions of Zimeta and your veterinarian will identify the underlying cause of your horse’s elevated body temperature. Response to Zimeta varies from horse to horse.

WHICH HORSES SHOULD NOT RECEIVE ZIMETA™?

Your horse should not be given Zimeta if it is:

- A non-steroidal anti-inflammatory drug for intravenous use in horses only.
- Has an allergic reaction to dipyrone, the active ingredient in Zimeta
- Has previously had an allergic reaction to any NOAls
- Is presently taking other NOAls or corticosteroids including but not limited to aspirin, phenylbutazone, flunixin meglumine, diclofenac, ketoprofen, firocoxib
- The safety of Zimeta has not been determined in horses less than three years of age or breeding horses, pregnant or lactating mares.

ZIMETA™ SHOULD BE GIVEN INTRAVENOUSLY TO HORSES ONLY

Zimeta is not for use in humans. Zimeta is not for use in horses intended for human food consumption. Do not use in any food producing animals, including lactating dairy animals. People should not take Zimeta. Keep Zimeta and all medications out of the reach of children. Consult your veterinarian in case of accidental ingestion by humans or accidental injection into humans.

WHAT TO TELL/ASK YOUR VETERINARIAN BEFORE GIVING ZIMETA

Talk to your veterinarian about:

- The signs of infection or inflammation you have observed in your horse, such as nasal discharge or coughing.
- Any history of previous allergies, such as reactions that you were treated for before Zimeta is prescribed.
- How often your horse may need to be examined by your veterinarian.
- The risks and benefits of using Zimeta.
- Other medical problems or allergies that your horse has now, or has had in the past.
- All medications your horse is taking or going to take in your horse, including those you can get without a prescription and any dietary supplements.
- Any previous allergies.
Tell your veterinarian if your horse has ever had the following medical problems:

- Any side effects from taking dipyrone (dipyrone injection) or other NSAIDs.
- Any increase in sweating, no racing variation, or known kidney disease.
- Any known liver disease.
- Any known stomach or gastrointestinal ulcers.
- Any known bleeding disorder.

Tell your veterinarian if your pet is a breed, or if your pet is pregnant or nursing a fetus.

WHAT ARE THE POSSIBLE SIDE EFFECTS THAT MAY OCCUR IN MY HORSE DURING ZIMETA THERAPY?

Some side effects may occur more often in horses receiving Zimeta than in other horses. Your veterinarian may be able to predict which side effects might occur based on your horse’s medical history. The following side effects have been reported in horses receiving Zimeta:

• Change in eating or drinking habits (frequency or amount consumed)
• Change in attitude or mood
• Unexplained bleeding
• Decreased appetite or weight loss
• Change in manure, such as diarrhea
• Change in behavior, such as depression
• Inappetence or loose manure
• Unexplained edema

It is important to stop therapy and contact your veterinarian if you think your horse has a medical problem or side effect while taking Zimeta. Kindred Biosciences, Inc. has additional guidance about possible side effects, talk with your veterinarian or call Kindred Biosciences at 1-888-668-2540.

CAN ZIMETA BE GIVEN WITH OTHER MEDICATIONS?

Zimeta should not be given at the same time as other NSAIDs (for example, aspirin, phenylbutazone, diclofenac, ketoprofen, flunixin, or flurbiprofen) or systemic corticosteroids (for example, prednisolone, dexamethasone, or triamcinolone).

WHAT ELSE SHOULD I KNOW ABOUT ZIMETA?

Consult your veterinarian if your horse receives more than the prescribed amount of 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 therapeutic dose). Twelve horses in the 0 mg/kg group were treated with saline alone as a control. No horses were treated with Zimeta at 30 mg/kg bodyweight or 60 mg/kg bodyweight. The results of this safety 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 safety phase was an open-label field study to evaluate the safety of Zimeta when administered intravenously at 30 mg/kg bodyweight to horses under field conditions. Eighty-seven horses from the first phase entered this phase. During the extended use 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, aged 5 to 22 years, with naturally occurring 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 pleruropneumonia; 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 affects 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 partial thromboplastin time (PTT). 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 abscession with hemmorhage, and potential and echymotic hemorrhage of the lungs. Overall, PT was statistically significantly prolonged for the horses in the 2X and 3X dose groups when compared to control horses (p<0.001). 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, ulcers were present on the 3X TID horse and two 1X TID horses. No erosions or ulcerations were identified on the 0 mg/kg group. Histopathology was consistent with 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 histopathologic changes were not associated with changes on gross necropsy, in pathologic or clinical signs of renal function.

For the evaluation 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 (TID) for 9 consecutive days. Horses in the control group were administered placebo (saline). The most common treatment-related adverse effects were anemia, 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 the potential for increased clotting time associated with the administration of Zimeta. A horse with pyrexia under field conditions. Eighty-seven horses from the first phase entered this phase. During the extended use 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.

Additional information on this study can be found in the EMEA/MRL/878/03-Final, the EMA/MRL/378/03-EF/3 and the EMA/MRL/257/03-MR/3 summaries. For a copy of the Safety Data Sheet (SDS) or to report adverse reactions contact Kindred Biosciences.

For your safety, Kindred Biosciences recommends that the horse receive no other medications in the 24 hours before or after Zimeta is administered.

Storage Information: Store at Controlled Room Temperature 20° and 25°C (68° and 77°F), with excursions permitted between 15° and 30°C (59° and 86°F). Protect from light.

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NDC 68078-245-01
Manufactured for:
Kindred Biosciences, Inc.
1555 Bayshore Hwy, Suite 200
Burlingame, CA 94010

For a copy of the Safety Data Sheet (SDS) or to report adverse reactions contact Kindred Biosciences.

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