zoetis

TECHNICAL SUMMARY

Draxxin® KP

(tulathromycin and ketoprofen injection)

INJECTABLE SOLUTION

- **Combines the reliability of DRAXXIN® Injectable Solution (tulathromycin injection) with the pyrexia-controlling potency of ketoprofen (a non-steroidal anti-inflammatory drug, NSAID).**
- **For treatment of BRD and control of pyrexia (fever).**
- **1.1 mL/100 lb body weight (BW) by subcutaneous (SC) injection.**
- **18-day pre-slaughter withdrawal.**

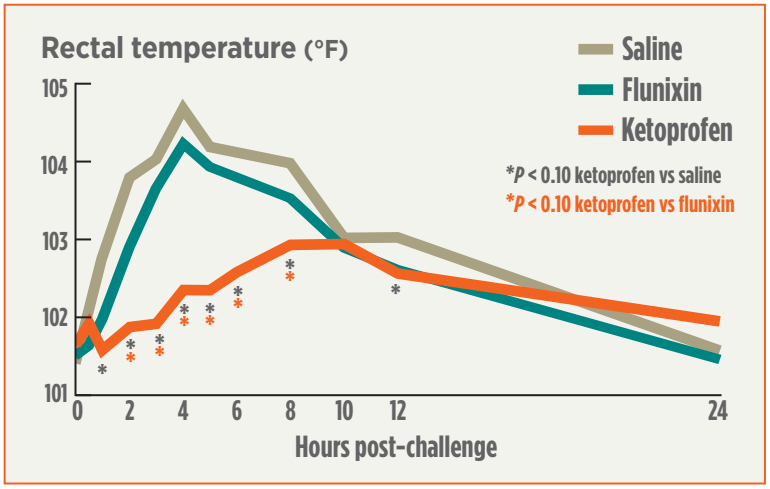
Ketoprofen pyrexia study[1]

Study Design

- Lipopolysaccharide (LPS, or 'endotoxin') is a component of Gram-negative bacteria and typically induces strong pyrexia responses in cattle.
- 48 healthy Holstein steers challenged SC with LPS at 5.0 µg/kg BW.
- Steers immediately randomized to 3 treatment groups (n=16/group) for single-dose NSAID treatment with either:
  - saline, control (SC);
  - flunixin meglumine (NSAID), 2.2 mg/kg BW (IV);
  - ketoprofen, 3 mg/kg BW (SC).
- Temperature responses monitored for 24 hours.

Results

- LPS challenge caused pyrexia spikes within 4 hours in both the saline control and flunixin groups.
- Compared to controls, ketoprofen significantly reduced ($P < 0.10$) rectal temperature at hours 1 through 8, and 12; flunixin reduced ($P < 0.10$) temperature at hours 1 and 2.
- Compared to flunixin, ketoprofen reduced ($P < 0.10$) temperature at hours 2 through 8.



Changes in rectal temperature over time for calves receiving saline, flunixin, or ketoprofen immediately after LPS challenge at 0 hours.

Ketoprofen was effective for pyrexia control, with benefits evident within 1 hour of treatment. Ketoprofen reduced pyrexia longer than flunixin.

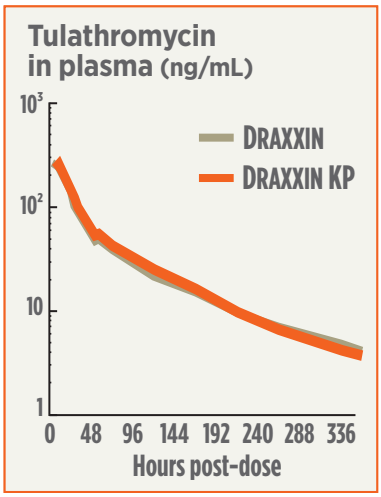
Pharmacokinetics study[2]

Study Design

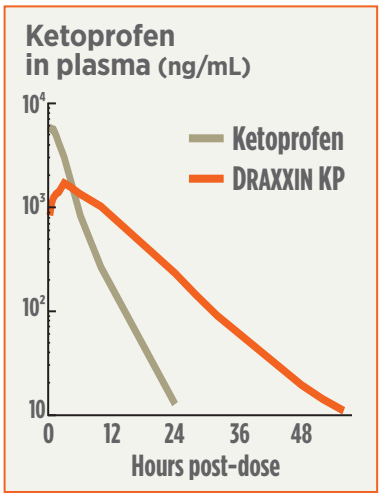
- Pharmacokinetics of the DRAXXIN KP combination (tulathromycin+ketoprofen) were compared with ketoprofen or DRAXXIN dosed alone.
- 60 Holstein steers randomized to 3 treatment groups (n=20/group) for single, label-dose SC treatment with either DRAXXIN, ketoprofen, or DRAXXIN KP.
- Plasma repeatedly assayed for tulathromycin and/or ketoprofen concentrations over a 15-day period.

Results

- ***Tulathromycin*** pharmacokinetics were ***similar*** whether delivered via DRAXXIN KP or DRAXXIN, thus meeting criteria for bioequivalence.
- ***Ketoprofen*** pharmacokinetics were ***different*** when delivered via DRAXXIN KP vs ketoprofen alone:
  - half-life longer with DRAXXIN KP (6.84 vs 2.86 h);
  - total ketoprofen exposure (AUC) 15% greater with DRAXXIN KP (26,458 vs 23,106 ng•h/mL);
  - peak concentration lower with DRAXXIN KP (C_{max} 2322 vs 6451 ng/mL).



Mean plasma concentrations of *tulathromycin* in cattle delivered via DRAXXIN or DRAXXIN KP.



Mean plasma concentrations of *ketoprofen* in cattle delivered via ketoprofen or DRAXXIN KP.

DRAXXIN® KP favorably extended the duration of NSAID exposure and drug clearance compared to ketoprofen alone.

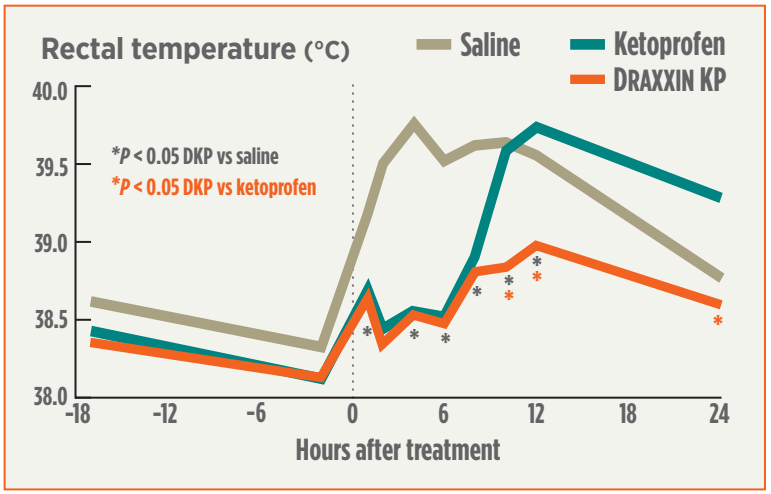
Duration of pyrexia-control effect[3]

Study Design

- 60 healthy Holstein steer calves challenged SC with LPS at 5.0 µg/kg BW.
- Within 30 minutes of challenge, steers randomized to 3 treatment groups (n=20/group) for single, label-dose SC treatment with either ketoprofen or DRAXXIN KP, or saline (control).
- Rectal temperature responses assessed for 24 hours; calves monitored for attitude or respiratory abnormalities.

Results

- Compared to controls, both DRAXXIN KP and ketoprofen significantly reduced ($P < 0.05$) rectal temperature beginning 1 hour post-challenge and continuing through 8 hours.
- DRAXXIN KP also significantly reduced ($P < 0.05$) temperature for hours 10 through 24 compared to ketoprofen alone, consistent with the longer ketoprofen terminal half-life provided by DRAXXIN KP.
- Higher numerical rates of normal attitude and respiration were maintained in the DRAXXIN KP group compared to the ketoprofen and control groups.



Rectal temperatures for animals subjected to LPS challenge on day 0 and treated with ketoprofen or DRAXXIN KP.

DRAXXIN® KP provided a longer duration of pyrexia control than ketoprofen alone, likely due to its favorable pharmacokinetic profile.

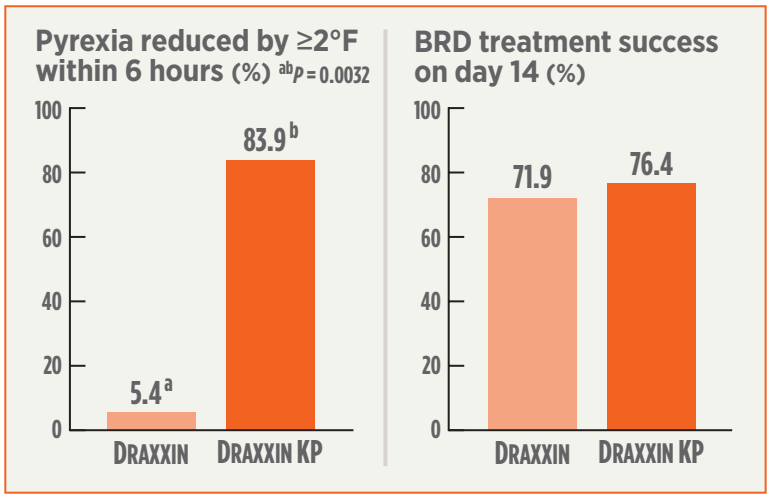
Treatment of naturally occurring BRD[4]

Study Design

- Field study conducted at 5 commercial feedyards in NE, ID, and CA. Crossbred, mixed-sex calves (328-717 lb) sourced from auctions in October/November.
- 819 animals with BRD (rectal temperature ≥104.5°F + abnormal attitude/respiratory scores) randomized to 3 treatment groups for SC single-dose treatment:
  - saline, control (n=273);
  - DRAXXIN (n=273);
  - DRAXXIN KP (n=273).
- BRD confirmed at all study sites (isolations of *M haemolytica, P multocida, H somni,* and *M bovis*).
- Major study parameters included pyrexia reduction within 6 hours of treatment, and BRD treatment success rate at 14 days (normal or mild depression and respiratory scores, and rectal temperature <104.5°F).

Results

- DRAXXIN KP reduced pyrexia (≥2°F drop by 6 h) in far more animals (83.9%; P = 0.0032) than conventional DRAXXIN (5.4%).
- Mean rectal temperature for the DRAXXIN KP group ***fell 2.7°F*** by 6 hours post-treatment (102.7°F) from the initial 105.4°F mean for all calves. This drop was significantly lower ($P \leq 0.0010$) than control (105.1°F) and DRAXXIN (104.8°F) groups.
- DRAXXIN KP provided excellent efficacy against BRD, non-inferior to conventional DRAXXIN.



Rates of pyrexia reduction by 6 hours post-treatment, and rates of BRD treatment success on day 14, for cattle treated with DRAXXIN or DRAXXIN KP.

DRAXXIN® KP reduced pyrexia in most animals soon after treatment. Mean body temperature dropped 2.7°F in just 6 hours.

DRAXXIN KP achieved excellent 14-day efficacy against BRD, non-inferior to conventional DRAXXIN.

Draxxin® KP

- **Combination of DRAXXIN, the #1 BRD anti-infective,[5] with ketoprofen, a well-established NSAID.**
- **Potent control of pyrexia that usually comes with BRD.**
- **Rapid onset of pyrexia reduction (as soon as 1 hour).**
- **Combination product extends duration of pyrexia reduction compared to ketoprofen alone.**
- **Combination increases the half-life and AUC of ketoprofen without affecting the excellent pharmacokinetics and efficacy of DRAXXIN.**
- **Bioequivalent to the conventional DRAXXIN formulation used for years.**
- **Same single-dose treatment claims against BRD bacterial pathogens.**
- **Same low dose-volume and short withdrawal time as DRAXXIN.**

IMPORTANT SAFETY INFORMATION: DRAXXIN KP has a pre-slaughter withdrawal time of 18 days in cattle. Not for use in female dairy cattle 1 year of age or older, including dry dairy cows. Not for use in beef calves less than 2 months of age, dairy calves, and veal calves. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in animals previously found to be hypersensitive to tulathromycin and ketoprofen. See full Prescribing Information.

Draxxin® KP

(tulathromycin and ketoprofen injection)
INJECTABLE SOLUTION

For subcutaneous injection

Antibiotic: 100 mg of Tulathromycin/mL

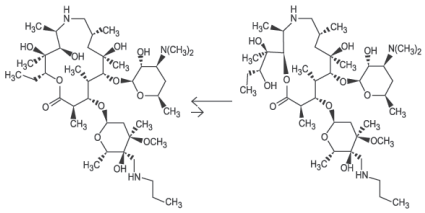
Non-Steroidal Anti-inflammatory Drug: 120 mg Ketoprofen/mL

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

DESCRIPTION

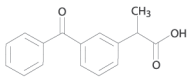
DRAXXIN KP (tulathromycin and ketoprofen injection) Injectable Solution is a ready to use sterile parenteral preparation containing tulathromycin, a semi-synthetic macrolide antibiotic of the subclass triamilide and ketoprofen a non-steroidal anti-inflammatory drug. **ACTIVE INGREDIENTS:** Each mL of DRAXXIN KP contains 100 mg of tulathromycin as a free base and 120 mg ketoprofen as a free acid in a 50% propylene glycol vehicle. **INACTIVE INGREDIENTS:** monothioglycerol (5 mg/mL), 2-pyrrolidone (70 mg/mL), citric acid (20 mg/mL) and sodium hydroxide/hydrochloric acid added to adjust pH. DRAXXIN KP contains an equilibrated mixture of two isomeric forms of tulathromycin in a 9:1 ratio and a racemic mixture of ketoprofen. The structures of the tulathromycin isomers and ketoprofen are shown below:

Figure 1. Tulathromycin structures



The chemical names of the tulathromycin isomers are (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribo-hexopyranosyl]oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]-oxy]-1-oxa-6-azacyclopentadecan-15-one and (2R,3R,6R,8R,9R,10S,11S,12R)-11-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino) methyl]-α-L-ribo-hexopyranosyl]oxy]-2-[(1S,2R)-1,2-dihydroxy-1-methylbutyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one, respectively.

Figure 2. Ketoprofen Structure



The chemical name of ketoprofen is 2-(3-Benzoylphenyl) propanoic acid.

INDICATIONS

Draxxin® KP is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni*, and *Mycoplasma bovis*, and control of pyrexia associated with BRD in beef steers, beef heifers, beef calves 2 months of age and older, beef bulls, dairy bulls, and replacement dairy heifers. Not for use in reproducing animals over one year of age, dairy calves, or veal calves.

DOSAGE AND ADMINISTRATION

Inject subcutaneously as a single dose in the neck at a dosage of 2.5 mg tulathromycin and 3 mg ketoprofen/kg (1.1 mL/100 lb) bodyweight (BW). Do not inject more than 10 mL per injection site. Use this product within 56 days of the first puncture and puncture a maximum of 20 times. If more than 20 punctures are anticipated, the use of automatic injection equipment or a repeater syringe 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.

Table 1. DRAXXIN KP Cattle Dosing Guide

Animal Weight (lb)	Dose Volume (mL)
150	1.7
200	2.3
250	2.8
300	3.4
350	4.0
400	4.5
500	5.7
600	6.8
700	8.0
800	9.1
900	10.2
1000	11.4

CONTRAINDICATIONS

The use of DRAXXIN KP Injection is contraindicated in animals previously found to be hypersensitive to tulathromycin and ketoprofen.

WITHDRAWAL PERIODS AND RESIDUE WARNINGS: Cattle must not be slaughtered for human consumption within 18 days following last treatment with this drug product. Not for use in female dairy cattle 1 year 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 or heifers. Not for use in beef calves less than 2 months of age, dairy calves, and veal calves. A withdrawal period has not been established for this product in pre-ruminating calves.

USER SAFETY WARNINGS:

NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.

The Safety Data Sheet (SDS) provides more detailed occupational safety information. To obtain a Safety Data Sheet contact Zoetis Inc. at 1-888-963-8471.

ANIMAL SAFETY WARNINGS and PRECAUTIONS

The effects of DRAXXIN KP on bovine reproductive performance, pregnancy, and lactation have not been determined. Not for use in reproducing animals over one year of age because reproductive safety testing has not been conducted. Administration of tulathromycin and ketoprofen injection may result in injection site swelling that appears the day after treatment and may persist for at least 32 days post-injection. This may result in trim loss of edible tissue at slaughter.

As a class, cyclo-oxygenase inhibitory NSAIDs (Ketoprofen) may be associated with gastrointestinal, hepatic 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. Use judiciously when renal impairment or gastric ulceration is suspected.

Since many NSAIDs possess the potential to induce gastrointestinal ulceration, concomitant use of DRAXXIN KP with other anti-inflammatory drugs, such as other NSAIDs and corticosteroids, should be avoided or closely monitored.

Discontinue use if fecal blood is observed.

ADVERSE REACTIONS

Repeated administration of NSAIDs can result in gastric or renal toxicity. Sensitivity to drug-associated adverse effects varies with the individual patient. Patients at greatest risk for toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with pre-existing gastric ulcers, renal, cardiovascular, and/or hepatic dysfunction.

CONTACT INFORMATION:

To report suspected adverse drug experiences, to obtain a Safety Data Sheet (SDS) or for technical assistance, contact Zoetis at (888) 963-8471. For additional information about adverse drug experience reporting for animal drugs, contact the FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY

Mechanism of Action

Ketoprofen is a propionic acid derivate and nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic effects. Ketoprofen inhibits the activity of the enzymes cyclo-oxygenase I and II, resulting in a decreased formation of precursors of prostaglandins and thromboxanes. Ketoprofen also causes a decrease in the formation of thromboxane A2 synthesis, by thromboxane synthase, thereby inhibiting platelet aggregation.

The principal mechanism of action of tulathromycin against bacteria involves direct inhibition of essential protein biosynthesis by selective binding to bacterial 50S ribosomal subunits. Tulathromycin acts by stimulating the dissociation of peptidyl-tRNA from the ribosome during the translocation process.

Clinical Pharmacology

In a GLP pharmacokinetic study, 60 cattle received one of 3 treatments: 2.5 mg tulathromycin/kg BW, 3 mg ketoprofen/kg BW or a combination of the two active ingredients (2.5 mg tulathromycin and 3 mg of ketoprofen/kg BW) via subcutaneous injection. Blood samples were obtained pre-dose and at 20 min, 40 min, 1, 1.5, 2, 3, 4, 6, 10, 24, 28, 32, 48, 52, 56, 72, 120, 168, 216, 264, 336, and 360 hours after dosing. The samples were analyzed using validated high-performance liquid chromatography-mass spectrometry (LC-MS/MS) methods for tulathromycin and ketoprofen concentrations. The rate of drug exposure was greater for the ketoprofen alone product.

The mean [±standard deviation (SD)] maximum plasma concentration (Cmax) and time to Cmax (tmax) was 6451 (±1342) ng/mL and 0.83 (±0.53) hr, respectively for ketoprofen alone compared to a mean (±SD) Cmax and tmax of 2322 (±1505) ng/mL and 4.0 (±2.93) hr, respectively, for ketoprofen in the combination product. However, the extent of drug exposure was slightly greater and terminal half life (t1/2) was longer for ketoprofen in the combination product. The mean (±SD) area under the drug concentration- time curve between times 0 and the last quantifiable concentration (AUC0-t(last)) was 26458 (±3605) ng*hr/mL for ketoprofen in the combination product and 23106 (±3500) for ng*hr/mL for ketoprofen alone. Similarly, the mean t 1/2 was 6.84 (±2.09) hr for ketoprofen in the combination product and 2.86 (±1.09) hr for ketoprofen alone. Although the mean (±SD) Cmax of tulathromycin in the combination group (373 (±105) ng/mL) was less than tulathromycin alone (653 (±261) ng/mL), based on mean (±SD) AUC0-t(last), the combination (13647 (±2577) ng*hr/mL) and tulathromycin alone (14088 (±4408) ng*hr/mL) groups had similar tulathromycin bioavailability.

Tulathromycin half life was also similar between the combination (93.3 (±27.9) hr) and tulathromycin alone (98.7 (±23.1) hr) groups.

MICROBIOLOGY

Based on data provided for the approval of Draxxin® (tulathromycin injection, NADA 141-244), tulathromycin has demonstrated *in vitro* activity against *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni*, and *Mycoplasma bovis*, four pathogens associated with BRD.

TARGET ANIMAL SAFETY

Thirty-two (16 male and 16 female) growing cattle were enrolled in a margin of safety study. Calves were injected subcutaneously with either saline, DRAXXIN KP at the label dose 2.5 mg tulathromycin/3 mg ketoprofen/kg BW, DRAXXIN KP at 3 times the label dose, or DRAXXIN KP at 5 times the label dose. Calves received three doses at a 14-day interval between doses. Daily clinical observations were conducted by a veterinarian as well as daily general health observations and injection site evaluations. Samples were collected for urinalysis, fecal occult blood, hematology, serum chemistry and coagulation and for pharmacokinetics. At the conclusion of the study, all animals were euthanized and necropsied for gross pathology and histopathology evaluation. Injection site lesion volumes for the first injection site was calculated. Injection site reactions were noted in all DRAXXIN KP-treated animals and the size and incidence of injection site lesions were greater in the 3X and 5X treatment groups.

Test article-related differences in serum chemistry parameters were lower alkaline phosphatase in the 5X group; lower albumin in the 3X and 5X groups; lower total protein (TP) and serum calcium in the 1X, 3X and 5X groups; and higher creatine kinase (CK) in the 1X, 3X, and 5X groups. The changes for serum calcium and albumin were considered clinically insignificant because all values were within the normal reference range on the days with statistical differences. The changes for TP were considered secondary to the differences in albumin and clinically insignificant because the albumin changes were considered clinically insignificant. In addition, the only TP values that were outside of the normal reference range were only 0.1 g/dL below the normal reference range. The differences in neutrophil values might be secondary to test article-associated injection site inflammation and the differences in CK values are directly associated with injection site reactions.There were non-quantifiable ketoprofen plasma concentrations prior to the second and third doses, while there was a modest accumulation for tulathromycin (mean ≤16.5%) with the 14-day dosing interval. There was dose proportional increase in tulathromycin AUC0-t(last) with an increase in dose, while there was slightly greater than dose proportional increase in ketoprofen AUC0-t(last). A single calf in Group T04 had test article-associated positive fecal occult blood samples on Days 15 and 29. Microscopic mucosal erosions of the pylorus of the abomasum were present in the 3X (2/8) and 5X (1/8) groups and was considered test article-related. Renal interstitial inflammation and minimal multifocal degeneration and regeneration occurred at similar incidence and severity in treated and control calves. Subcutaneous injection of cattle with tulathromycin- ketoprofen at the label dose was well tolerated.

EFFECTIVENESS

A multi-location field study was conducted to evaluate the effectiveness of Draxxin® KP for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni*, and *Mycoplasma bovis*, and control of pyrexia associated with BRD. A total of 819 cattle with clinical signs of BRD (moderate depression and respiratory distress, and a rectal temperature ≥104.5 °F) were enrolled and treated with either saline (0.025 mL/kg BW), tulathromycin (2.5 mg/kg BW) or Draxxin® KP (2.5 mg tulathromycin/kg BW and 3 mg ketoprofen/kg BW) administered by subcutaneous injection. Rectal temperatures were measured six hours later and animals were observed for clinical signs of BRD through 14 days post-treatment. An animal was classified as a treatment success for treatment of BRD if it was not classified as a failure prior to Day 14, and had normal or mild depression and respiratory distress scores and a rectal temperature <104.5 °F on Day 14. An animal was classified as a treatment success for control of pyrexia associated with BRD if it displayed a ≥2 °F reduction in rectal temperature at 6-hours post-treatment compared to pre-treatment. The Draxxin® KP-treated group had a significantly different (P=0.0020) and numerically higher success rate (76.2%) for the treatment of BRD compared to the saline-treated group (31.6%), and the success rate in the Draxxin® KP-treated group was statistically non-inferior to that in the group receiving tulathromycin alone. The success rate (back-transformed estimate) for pyrexia associated with BRD in the Draxxin® KP-treated group was significantly different (P=0.0010) and numerically higher (83.8%) at 6 hours post-treatment than the success rate in the saline-treated group (2.4%). The success rate (back-transformed estimate) for pyrexia associated with BRD in the Draxxin® KP-treated group was significantly different (P=0.0032) and numerically higher (83.9%) at 6 hours post-treatment than the success rate in the tulathromycin-treated group (5.4%). A sufficient number of *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni*, and *Mycoplasma bovis* were isolated from cattle in the study to demonstrate that these BRD pathogens were contributing to the observed disease.

HOW SUPPLIED

DRAXXIN KP Injection is available in the following package sizes:
50 mL vial
100 mL vial
250 mL vial
500 mL vial

STORAGE CONDITIONS

Store at or below 25°C (77°F), with excursions up to 40°C (104°F). Protect from freezing.

APPROVED BY FDA under NADA # 141-543

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Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Product of Spain

May 2021

40028876/40028876/40028872/40028868A&P

References

1. Data on file, Study Report No. AR32W-US-14-283, Zoetis LLC.
2. Data on file, Study Report No. A431N-US-16-418, Zoetis LLC.
3. Data on file, Study Report No. A136R-US-16-508, Zoetis LLC.
4. Data on file, Study Report No. A131C-US-17-531, Zoetis LLC.
5. DRAXXIN was highest in sales in the anti-infective therapeutic category, per Animalytix Segment Data Ending MAT June 2021.

TAKE TIME
OBSERVE LABEL DIRECTIONS

zoetis