HFA-305 Division of Dockets Management

Date of Approval : MAR 2 3 2005

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 065-506

COMBI-PEN-48

(Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension)

This supplement provides for a change in the trade name from COMBICILLIN-AG to COMBI-PEN-48 and the addition of the statements "A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal." to the warning section of the product labeling.

Sponsored by:

Cross Vetpharm Group Ltd.
Broomhill Rd., Tallaght
Dublin 24, Ireland

2005-065-506

F 0131

1. GENERAL INFORMATION:

a.	File Number:	NADA 065-506
b.	Sponsor:	Cross Vetpharm Group Ltd. Broomhill Rd., Tallaght Dublin 24, Ireland Drug Labeler Code: 061623
c.	Established Name:	Penicillin G Benzathine and Penicillin G Procaine
d.	Proprietary Names:	COMBICILLIN-AG (OTC label) trade name change to COMBI-PEN-48; (COMBICILLIN (Rx label) trade name is not being changed; this product is not currently being marketed.)
e.	Dosage Form:	Injectable sterile aqueous suspension
f.	How Supplied:	100, 250, and 500 mL, multi-dose vials
g.	How Dispensed:	OTC
h.	Amount of Active Ingredients:	150,000 units per mL of penicillin G benzathine and 150,000 units per mL of penicillin G procaine
i.	Route of Administration:	Subcutaneous (SC)
j.	Species/Class:	Beef cattle
k.	Recommended Dosage:	2 mL per 150 lb body weight given subcutaneously only (2000 units penicillin G procaine and 2000 units penicillin G benzathine per lb of body weight). Treatment should be repeated in 48 hours.
l.	Pharmacological Category:	Antimicrobial
m.	Indications:	The product is indicated for the treatment of the following bacterial infections in beef cattle due to penicillin-susceptible microorganisms that are susceptible to the serum levels common to this particular dosage form, such as: 1. Bacterial pneumonia (shipping fever complex) (*Streptococcus* spp., *Corynebacterium pyogenes*, and *Staphylococcus aureus*) 2. Upper respiratory infections such as rhinitis or

pharyngitis (*Corynebacterium pyogenes*)

3. Blackleg (*Clostridium chauvoei*)

n. Effect of Supplement: This supplement provides for a change in the proprietary name on the OTC label product from COMBICILLIN-AG to COMBI-PEN-48 and the addition of the statements "A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal." to the warning section of the product labeling.

2. *DRUG EFFECTIVENESS:*

No new effectiveness data were required for the approval of this supplement. The product's effectiveness was established in the original Freedom of Information (FOI) Summary dated November 8, 1993 (Folder B).

3. *TARGET ANIMAL SAFETY:*

No new target animal safety data were required for the approval of this supplement. The product's target animal safety was established in the original FOI Summary dated November 8, 1993 (Folder B).

4. *HUMAN FOOD SAFETY:*

No further human safety data were required from the original approval as discussed in the parent NADA 65-506 FOI Summary dated November 8, 1993. There is a 30-day withdrawal period for slaughter and a withdrawal period has not been established for pre-ruminating calves.

5. *AGENCY CONCLUSIONS:*

The information submitted in support of this supplemental NADA satisfies the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations and provides for a change in the proprietary name for the OTC label product.

The following has been added to the residue information section of the labeling: "A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal".

The Agency has concluded that this product may retain over-the-counter marketing status because adequate directions for use have been written for the layperson and the conditions of use prescribed on the label are likely to be followed in practice.

In accordance with 21 CFR 514.106(b)(2)(ix), this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of

this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval for food-producing animals does not qualify for marketing exclusivity because the application does not contain substantial evidence of the effectiveness of the drugs involved, any studies of animal safety, or, in the case of food-producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant.

No patents were submitted with this application.

6. *ATTACHMENTS:*

Facsimile Labeling is attached as indicated below:

Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension product insert
COMBI-PEN-48 100 mL bottle label
COMBI-PEN-48 250 mL bottle label
COMBI-PEN-48 500 mL bottle label

Jan 4, 2005

Each mL of suspension contains:

Penicillin G benzathine	150,000 units
Penicillin G procaine	150,000 units
Lecithin	11.7 mg
Sodium formaldehyde sulfoxylate	1.75 mg
Methylparaben (as preservative)	1.20 mg
Propylparaben (as preservative)	0.14 mg
Tween 40	5.19 mg
Span 40	11.3 mg
Sodium citrate anhydrous	3.96 mg
Procaine hydrochloride	20 mg
Sodium carboxymethylcellulose	1.04 mg
Water for injection	q.s.

STORE UNDER REFRIGERATION
BETWEEN 2°- 8°C (36°-46°F)
PROTECT FROM FREEZING

TAKE TIME — OBSERVE LABEL DIRECTIONS

Bimeda, Inc. is a Division of Cross Vetpharm Group Ltd
Product No. 1CCM301
8CCM301-1104

Combi-Pen-48®

(Penicillin G Benzathine and
Penicillin G Procaine Injectable Suspension)

[illegible]
[illegible] units per mL
[illegible] Use in Beef Cattle Only
[illegible] Multiple Dose Vial
Restricted Drug (California): Use only as directed.
[illegible] APPROVED BY FDA

Net Contents: 100 mL

Manufactured by
Bimeda, Inc.
Irwindale, CA 91706

Bimeda

See Insert For Directions
WARM TO ROOM TEMPERATURE AND SHAKE WELL BEFORE USING
Beef Cattle: 2 mL per 150 lb. body weight, given subcutaneously only.
FOR ANIMAL USE ONLY
KEEP OUT OF REACH OF CHILDREN

WARNING:
Do not inject intramuscularly.
Beef cattle should be withheld from slaughter for food use for thirty (30) days following last treatment. Treatment in beef cattle must be limited to two (2) doses.
A withdrawal period has not been established for this product in pre-ruminating calves.
Do not use in calves to be processed for veal.

Combi-Pen-48 is a Registered Trademark of Bimeda, Inc.

Lot No./Exp. Date:

8 99855 60003 5

PMS 877

PMS 259

Black

BKG1

Jan 4, 2005

Each mL of suspension contains:

Penicillin G benzathine	150,000 units
Penicillin G procaine	150,000 units
Lecithin	11.7 mg
Sodium formaldehyde sulfoxylate	1.75 mg
Methylparaben (as preservative)	1.20 mg
Propylparaben (as preservative)	0.14 mg
Tween 40	8.19 mg
Span 40	11.3 mg
Sodium citrate anhydrous	3.98 mg
Procaine hydrochloride	20 mg
Sodium carboxymethylcellulose	1.04 mg
Water for Injection	q.s.

TAKE TIME OBSERVE LABEL DIRECTIONS

Bimeda, Inc. is a Subsidiary of Cross Vetpharm Group Ltd.

Product No. 1COM307
SCOM305 1-04

Combi-Pen-48®

(Penicillin G Benzathine and
Penicillin G Procaine Injectable Suspension)

Injectable Suspension
Sterile
300,000 units per mL
For Subcutaneous Use in Beef Cattle Only
Sterile, Multiple Dose Vial

Restricted Drug (California): Use Only as Directed.

NADA 065-506, APPROVED BY FDA

Net Contents: 250 mL

Manufactured by
Bimeda, Inc.
Irwindale, CA 91706

See Insert For Directions
WARM TO ROOM TEMPERATURE AND SHAKE WELL BEFORE USING

Beef Cattle: 2 mL per 150 lb. body weight, given subcutaneously only.

FOR ANIMAL USE ONLY
KEEP OUT OF REACH OF CHILDREN

WARNING:
Do not inject intramuscularly.
Beef cattle should be withheld from slaughter for food use for thirty (30) days following last treatment. Treatment in beef cattle must be limited to two (2) doses. A withdrawal period has not been established for this product in pre-ruminating calves.
Do not use in calves to be processed for veal.

STORE UNDER REFRIGERATION
BETWEEN 2°- 8°C (36°-46°F)
PROTECT FROM FREEZING

Combi-Pen-48 is a Registered Trademark of Bimeda, Inc

Lot No.:/Exp. Date:

UPC CODE
8 99855 60004 2

PMS 877

PMS 259

Black

Jan 4, 2005

Each mL of suspension contains:

Penicillin G benzathine	150,000 units
Penicillin G procaine	150,000 units
Lecithin	11.7 mg
Sodium formaldehyde sulfoxylate	1.75 mg
Methylparaben (as preservative)	1.20 mg
Propylparaben (as preservative)	0.14 mg
Tween 40	8.19 mg
Span 40	11.3 mg
Sodium citrate anhydrous	3.98 mg
Procaine hydrochloride	20 mg
Sodium carboxymethylcellulose	1.04 mg
Water for Injection	q.s.

TAKE TIME OBSERVE LABEL DIRECTIONS

Bimeda, Inc. is a Division of Cross Vetpharm Group Ltd.

Product No.: 1COM303
8COM306-1104

Combi-Pen-48®

(Penicillin G Benzathine and
Penicillin G Procaine Injectable Suspension)

Aqueous Suspension
Antibiotic
300,000 units per mL
For Subcutaneous Use in Beef Cattle Only
Sterile, Multiple Dose Vial

Restricted Drug (California): Use Only as Directed.

NADA 065-506, APPROVED BY FDA

Net Contents: 500 mL

Manufactured by
Bimeda, Inc.
Irwindale, CA 91706

Bimeda

See Insert For Directions

WARM TO ROOM TEMPERATURE AND SHAKE WELL BEFORE USING

Beef Cattle: 2 mL per 150 lb body weight, given subcutaneously only.

FOR ANIMAL USE ONLY
KEEP OUT OF REACH OF CHILDREN

WARNING:
Do not inject intramuscularly.
Beef cattle should be withheld from slaughter for food use for thirty (30) days following last treatment. Treatment in beef cattle must be limited to two (2) doses. A withdrawal period has not been established for this product in pre-ruminating calves.
Do not use in calves to be processed for veal.

STORE UNDER REFRIGERATION
BETWEEN 2°- 8°C (36°-46°F)
PROTECT FROM FREEZING

Combi-Pen-48 is a Registered Trademark of Bimeda, Inc.

Lot No.:/Exp. Date:

UPC CODE
8 99855 60005 9

PMS 259

PRINTED IN BLUE

PENICILLIN G BENZATHINE AND PENICILLIN G PROCAINE INJECTABLE SUSPENSION

FOR ANIMAL USE ONLY

FOR SUBCUTANEOUS USE ONLY - FOR USE IN BEEF CATTLE ONLY

DESCRIPTION: Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension is available as an aqueous suspension in 100-mL, 250-mL and 500-mL multiple-dose vials Each mL contains 150,000 units penicillin G benzathine, 150,000 units penicillin G procaine, 11 7 mg lecithin, 1 75 mg sodium formaldehyde sulfoxylate, 1.20 mg methylparaben, 0.14 mg propylparaben, 8.19 mg Tween 40, 11.3 mg Span 40, 3 98 mg sodium citrate (anhydrous), 20 mg procaine hydrochloride, 1.04 mg sodium carboxymethylcellulose, Water for Injection, q.s

ACTION: Penicillin G is an antibiotic which shows a marked bactericidal effect against certain organisms during their growth phase. It is relatively specific in its action against gram-positive bacteria but is usually ineffective against gram-negative organisms.

It is normally recommended that any bacterial infection be treated as early as possible and with a dosage that will give effective blood levels. Although the recommended dosage of this product will give longer detectable penicillin blood levels than penicillin G procaine alone, it is recommended that a second dose be administered at 48 hours when treating a penicillin-susceptible bacterial infection

The use of antibiotics in the management of disease is based on an accurate diagnosis and an adequate course of treatment. When properly used in the treatment of diseases caused by penicillin-susceptible organisms, most animals treated with the product will show a noticeable improvement within 24 to 48 hours. If improvement does not occur within this period of time, the diagnosis and course of treatment should be re-evaluated It is recommended that the diagnosis and treatment of animal diseases be carried out by a veterinarian. Since many diseases look alike but require different types of treatment, the use of professional veterinary and laboratory services can reduce treatment time, costs and needless losses Good housing, sanitation and nutrition are important in the maintenance of healthy animals and are essential in the treatment of disease

WARNING: Beef cattle should be withheld from slaughter for food use for 30 days following the last treatment Treatment in beef cattle must be limited to two (2) doses, by subcutaneous injection only Do not inject intramuscularly

A withdrawal period has not been established for this product in pre-ruminating calves Do not use in calves to be processed for veal.

INDICATIONS: This product is indicated for the treatment of the following bacterial infections in beef cattle due to penicillin-susceptible microorganisms that are susceptible to the serum levels common to this particular dosage form, such as

1 Bacterial Pneumonia (shipping fever complex) (Streptococcus sop., Corynebacterium pyrogenes, Staphylococcus aureus)
2 Upper Respiratory Infections such as rhinitis or pharyngitis (Corynebacterium pyrogenes)
3 Blackleg (Clostridium chauvoi)

PRECAUTIONS: Exceeding the recommended doses and dosage levels may result in antibiotic residues beyond the withdrawal time Do not inject this product intramuscularly

Penicillin G is a substance of low toxicity However, side effects, or so-called allergic or anaphylactic reactions - sometimes fatal, have been known to occur in animals hypersensitive to penicillin and procaine. Such reactions can occur unpredictably with varying intensity Animals administered penicillin G should be kept under close observation for at least one-half hour. Should allergic or anaphylactic reactions occur, discontinue use of the product and immediately administer epinephrine following the manufacturer's recommendations and call a veterinarian

As with all antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi A lack of response by the treated animal, or the development of new signs or symptoms suggests that an overgrowth of non-susceptible organisms has occurred In such instances, consult your veterinarian

Since bacterial drugs may interfere with the bacteriostatic action of tetracyclines, it is advisable to avoid giving penicillin in conjunction with tetracyclines

The product should be stored between 2°-8°C (36°-46°F) Avoid freezing Warm to room temperature, and shake well before using.

ADMINISTRATION: The recommended dosage for beef cattle should be administered by subcutaneous injection only Failure to use the subcutaneous route of administration may result in antibiotic residues in meat beyond the withdrawal time

DOSAGE

Beef cattle: 2mL per 150 lb body weight given subcutaneously only (2000 units penicillin G procaine and 2000 units penicillin G benzathine per lb body weight) Treatment should be repeated in 48 hours

IMPORTANT: Treatment in beef cattle should be limited to two (2) doses given by subcutaneous injection only

DIRECTIONS FOR USE: A thoroughly cleaned, sterile needle and syringe should be used for each injection (needles and syringes may be sterilized by boiling in water for 15 minutes)

Before withdrawing the solution from the bottle, disinfect the rubber cap on the bottle with a suitable disinfectant, such as 70 percent alcohol The injection site should be similarly cleaned with the disinfectant Needles of 14 to 16 gauge, and not more than 1 inch long are adequate for injections

A subcutaneous injection should be made by pinching up a fold of the skin between the thumb and forefinger The mid-neck region is the preferred injection site Insert the needle under the fold in a direction approximately parallel to the surface of the body When the needle is inserted in this manner the medication will be delivered underneath the skin between the skin and the muscles Proper restraint such as the use of a chute and nose lead is needed for proper administration of the product

STORE BETWEEN 2°-8°C (36°-46°F). AVOID FREEZING.
SHAKE WELL BEFORE USING. FOR ANIMAL USE ONLY.
RESTRICTED DRUG (UNDER CALIFORNIA LAW). USE ONLY AS DIRECTED

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