Date of Approval: November 10, 2014

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 034-267

GENTOCIN DURAFILM

(Gentamicin Sulfate and Betamethasone) Sterile Ophthalmic Solution

GENTOCIN DURAFILM Ophthalmic Solution is indicated for the treatment of external eye infections and inflammation in dogs.

The effect of the supplement is to provide a new product formulation.

Sponsored by:

Intervet Inc

TABLE OF CONTENTS

I. GENERAL INFORMATION:

A. File Number

NADA 034-267

B. Sponsor

Intervet Inc.,
556 Morris Avenue
Summit, NJ 07901

Drug labeler code: 000061

C. Proprietary Name

GENTOCIN DURAFILM

D. Established Name

Gentamicin Sulfate and Betamethasone Acetate

E. Pharmacological Category

Antibacterial and anti-inflammatory

F. Dosage Form

Ophthalmic Solution

G. Amount of Active Ingredient

3 mg/ml gentamicin base, 1 mg/ml betamethasone acetate

H. How Supplied

5 mL plastic vials

I. Dispensing Status

Rx

J. Dosage Regimen

GENTOCIN DURAFILM Ophthalmic Solution should, in each instance, be administered to meet the specific needs of the individual case. One or two drops of the solution may be instilled into the conjunctival sac three or four times a day. Thereafter, the frequency of the dosage may be reduced but care should be taken not to discontinue therapy prematurely. In chronic conditions, withdrawal of treatment should be carried out by gradually decreasing the frequency of application.

K. Route of Administration

Topical Ophthalmic

L. Species/Class

Dogs

M. Indication

GENTOCIN DURAFILM Ophthalmic Solution is indicated for the treatment of external eye infections and inflammation in dogs. Clinical reports indicate it is useful for the management of some cases of pigmentary keratitis and pannus. Temporary remission of some of the pathological lesions of the aforementioned conditions have been noted following therapy with GENTOCIN DURAFILM Ophthalmic Solution.

N. Effect of Supplement

The effect of the supplement is to provide a new product formulation.

II. EFFECTIVENESS

CVM did not require effectiveness studies for this supplemental approval. The change in the formulation from Incrocas 30 (polyoxyl 32 castor oil) to Cremophor ELP (polyoxyl 35 castor oil) is not expected to impact the effectiveness of the product. These two excipients are from the same chemical family and are close in chemical structure; therefore, they are expected to behave similarly in the formulation.

III. TARGET ANIMAL SAFETY

A. Margin of Safety Study (Study #S13140)

1. Study Number: S13140
2. Study Title: GENTOCIN DURAFILM: A 5-Day Pilot Target Animal Safety Study in Dogs to Evaluate the Safety of an Ophthalmic Drug Product
3. Location: Charles River Laboratories, Ohio, USA
4. Purpose: The objective of this study was to evaluate the safety of a new formulation of Gentocin Durafilm formulated using Cremophor ELP as an excipient.
5. Study Design:
    a. Study Animals: Sixteen 5-month old Beagle dogs

b. Experimental Design: GENTOCIN DURAFILM was administered to healthy Beagle dogs (4 dogs/sex), 4 times daily, at a dose of 6 drops/eye (3X maximum therapeutic daily dose). The control group (4 dogs/sex) received 6 drops of sterile saline/eye 4 times daily (0X).

c. Route of Administration: Topical Ophthalmic

d. Measurements and Observations: Cage side observations were performed once daily, beginning on the day of animal receipt and throughout the dosing phase. The animals were removed from the cage and a detailed clinical observation was performed once to four times daily throughout the study. Ocular examinations were performed daily throughout the study. Each animal was weighed on Days -4, -1, 2, and 6. Food consumption was quantitatively measured for each animal daily, beginning Day -4 through Day 6. Detailed veterinary physical examinations were performed on Days -5 and -1, and at approximately 1 hour after the first ocular instillation on Days 2 and 5. Ophthalmic examinations were performed by a board-certified veterinary ophthalmologist once during the acclimation phase (Day -8) and on Day 5. Clinical pathology (including hematology, coagulation parameters, clinical chemistries, urinalysis, and fecal examination) was collected on Day -2 and Day 6.

e. Results: A serous ocular discharge was observed in 7 out of 8 dogs in the GENTOCIN DURAFILM treatment group (3X group). The finding resolved within a few hours of dosing. Bilateral scleral redness was observed in 5 out of 8 dogs from the 3X group. The redness persisted in the three 3X males after dosing was discontinued, but resolved within 72 hours of dosing cessation.

A decrease in urine specific gravity and polyuria was identified in the 3X group dogs on Day 6 of the study. Polyuria is consistent for dogs undergoing corticosteroid therapy.

Changes in hematological parameters in dogs in the GENTOCIN DURAFILM treatment group included neutrophilia, elevated platelet counts, eosinopenia, and a reduced reticulocyte count. These hematological changes are consistent for dogs undergoing corticosteroid therapy. The reduced reticulocyte count observed in the dogs may be attributed to gentamicin in the drug product rather than a non-regenerative anemic response.

Alanine aminotransferase, alkaline phosphatase, and γ-glutamyl transferase were increased after 5 days of administration of GENTOCIN DURAFILM. The increase is attributed to steroid administration and due to an enzyme induction rather than hepatocellular or hepatobiliary damage. Administration of GENTOCIN DURAFILM also resulted in an increase in triglyceride, albumin, globulin, and total protein levels. Creatine kinase levels were decreased. These serum chemistry changes are consistent for dogs undergoing steroid therapy.

f. Conclusion: The results of this study demonstrate that the new formulation of GENTOCIN DURAFILM was well tolerated when ophthalmically administered to dogs 4 times daily at doses of 3 times the clinical dose for 5 consecutive days.

B. Margin of Safety Study (Study #S13074)

1. Title: GENTOCIN DURAFILM: A Target Animal Safety Study in Dogs to Evaluate the Safety of an Ophthalmic Drug Product

2. Location: Charles River Laboratories, Ohio, USA

3. Purpose: The objective of this study was to evaluate the safety of a new formulation of GENTOCIN DURAFILM formulated using Cremophor ELP as an excipient.

4. Study Design:

a. Study Animals: 32 Beagle dogs which were 5 months old and weighed between 5.9 and 8.7 kg; 4 males and 4 females per group.

b. Experimental Design: GENTOCIN DURAFILM was administered four times daily for 14 consecutive days at a dose of 2 drops/eye (1X maximum therapeutic daily dose), 4 drops/eye (2X maximum therapeutic daily dose), and 6 drops/eye (3X maximum therapeutic daily dose). The control group received 6 drops of sterile saline/eye four times daily (0X). Each group was randomly assigned 4 male and 4 females dogs for the study.

c. Route of Administration: Topical Ophthalmic

d. Measurement and Observations: The animals were observed for general health/mortality and morbidity twice daily, once in the morning and once in the afternoon, throughout the study. Detailed clinical observations were performed once to twice daily throughout the study. Ocular observations were performed once to three times daily throughout the study. On Study Day 14, both eyes were macroscopically examined with the aid of an auxiliary light source for signs of irritation following a modified Draize scoring criteria. Each animal was weighed on Days -7, -1, 2, 5, 8, 11, 14, and 17. Food consumption was quantitatively measured for each animal daily, beginning Day -7 through Day 17. Detailed veterinary physical examinations were performed on Days -7 and -1, and at approximately 1 hour after the first ocular instillation on Days 2, 7, and 14. Ophthalmic examinations were performed by a board-certified veterinary ophthalmologist once during the acclimation phase (Day -9) and on Day 14 (2 to 6 hours after first ocular instillation). The examinations were conducted using a hand held slit lamp and indirect ophthalmoscope. Electrocardiogram (ECG) measurements were obtained once during the acclimation phase (Day -11) and on Day 14 (2 to 6 hours after first ocular instillation #1). Clinical Pathology (including hematology, coagulation parameters, clinical chemistries, urinalysis, and fecal examination) was collected on Days -10, -2, 2, and 15.

e. Statistical Analysis: All statistical comparisons of main (treatment) effects and treatment and time interactions were performed at the 0.1 level of significance; treatment and sex interactions were performed at the 0.1 level of significance and treatment and time and sex interactions were performed at the 0.05 level of significance using SAS PROC MIXED Version 9.1 or higher by the Principal Investigator. All continuous variables were analyzed using a mixed model. Ordinal variables were analyzed using contingency table analysis. The data from Study Days -7 to -1 were used as the covariate, where applicable, in the statistical analysis. If there were multiple observations available from the pretreatment period, then the mean of the pretreatment observations (baseline) was considered as a covariate. For continuous variables that were repeatedly measured and graphed, such as clinical pathology parameters, reference ranges used during the final animal selection process were indicated as reference range lines on the graphs of the data, as appropriate. The individual animal was the experimental unit for responses measured once and the time interval of an animal was the experimental unit. Statistical analysis was performed for the following parameters: body weights, food consumption, body temperature, heart rate, respiratory rate, blood pressure, Draize score, hematology (all parameters except peripheral smear data), serum chemistry, coagulation, urinalysis (pH and specific gravity only).

f. Results: A serous ocular discharge was observed in dogs administered GENTOCIN DURAFILM in a dose-related manner that resolved within a few hours of dosing. Bilateral scleral redness was seen in the 2X (1 of 8 dogs) and 3X (5 of 8 dogs) groups between Days 4-8; the redness spontaneously resolved.

Polyuria and decreased urine specific gravity was evident in 1 of 8 dogs in the 3X group on Day 2. Polyuria accompanied by decreased urine specific gravity was evident in a dose proportional manner in all three treatment groups after 14 days of dosing. Three of eight dogs had polyuria in the 1X group. Most dogs in both the 2X (7 of 8 dogs) and 3X (8 of 8 dogs) groups exhibited polyuria. Polyuria is a side-effect of corticosteroid therapy in dogs.

Dogs administered GENTOCIN DURAFILM had increased food consumption compared to dogs in the control group.

Changes in hematological parameters included neutrophilia, lymphopenia, and eosinopenia. These hematological changes are consistently observed in dogs undergoing corticosteroid therapy in a clinical scenario. A reduced reticulocyte count was observed in the dogs administered GENTOCIN DURAFILM and may be attributable to the gentamicin component of the drug product.

Alanine aminotransferase, alkaline phosphatase, and γ-glutamyl transferase were increased after 14 days of administration of GENTOCIN DURAFILM. The increase is attributed to steroid therapy and due to an enzyme induction rather than hepatocellular or hepatobiliary damage. GENTOCIN DURAFILM administration also resulted in an increase in

triglyceride, albumin, globulin, and total protein levels. Creatine kinase levels were decreased. These serum chemistry changes are consistent for dogs undergoing steroid therapy.

The changes seen in the hematological and clinical chemistry parameters were of minimal severity and were not accompanied by any correlating clinical signs or complications during or after administration of GENTOCIN DURAFILM.

g. Conclusion: The results of this study showed that the new formulation of GENTOCIN DURAFILM was well tolerated when ophthalmically administered to dogs 4 times daily for 14 days.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this supplemental NADA.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to GENTOCIN DURAFILM Ophthalmic Solution:

Not for human use. Keep this and all drugs out of the reach of children.

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that GENTOCIN DURAFILM, when used according to the label, is safe and effective for the treatment of external eye infections and inflammation in dogs.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly diagnose external eye infections and inflammation, to prescribe appropriate treatment, and to monitor the safe use of the product, including treatment of any adverse reactions.

B. Exclusivity

This supplemental approval for GENTOCIN DURAFILM qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act because the supplemental approval included safety studies. This exclusivity begins as of the date of our approval letter and only applies to the new product formulation that is approved in the supplemental application.

C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.