Approval Date: February 21, 1991

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 042-841

B. Sponsor

Fort Dodge Laboratories
Division of American Home Products
800 5th Street NW
Ford Dodge, IA 50501-0518

C. Proprietary Name

Amforol® Veterinary Oral Tablets

D. Established Name

kanamycin, pectin, bismuth subcarbonate, activated attapulgite (aluminum magnesium silicate)

E. Dispensing Status

OTC

F. Route of Administration

Oral

G. Effect of Supplement

This supplement provides for a revised formulation for Amforo; Veterinary Oral Tablets without aminopentamide hydrogen sulfate. The following issues are addressed.

II. DOSE OF AMINOPENTAMIDE IN ORIGINAL FORMULATION

Aminopentamide is an antispasmodic and anticholinergic agent which reduces peristalsis thereby reducing propulsive activity. The amount of aminopentamide in Amforol's original formulation was 0.033 mg per tablet, only 1/6 to 1/12 of the dose recommended when aminopentamide alone is given orally to the dog.

III. RATIONALE FOR REMOVING AMINOPENTAMIDE

In recent years, clinicians have modified their recommendations for the treatment of acute non-specific diarrhea. Published literature now suggests that the use of antispasmodics / anticholinergics is not indicated in the routine treatment of small animals with diarrhea. They may produce intractable diarrhea due to ileus.

In cases of spasmodic diarrhea, antispasmodics / anticholinergics may result in a therapeutic benefit. However, the use of anticholinergics should be restricted to documented

cases of spasmodic diarrhea since their routine use in other types of diarrhea may impair normal motility.

The following references suggest that anticholinergic drugs like aminopentamide may be contraindicated in the routine management of diarrhea.

A. Wilson, R. C.: Antimotility drugs used in treatment of diarrhea. JAVMA, 180:776-777, 1982.

B. Strombeck, D. R.: Management of diarrhea: Motility modifiers and adjunct therapy. IN, Current Veterinary Therapy, VII, 1980.

C. Chiapella A. M.: Treatment of Intestinal Disease. IN, The Veterinary Clinics of North America, 567-584, August 1983.

D. Reves R., et al: Failure to Demonstrate Effectiveness of an Anticholinergic Drug in the Symptomatic Treatment of Acute Travelers Diarrhea. 5:223-227, 1983.

IV. EFFECTIVENESS

The removal of aminopentamide hydrogen sulfate which was present at subtherapeutic levels will not have an adverse effect on the products's efficacy. The new formulation provides:

- Kanamycin, a broad-spectrum antibiotic
- Pectin
- Attapulgite (aluminum magnesium silicate), an activated clay mineral
- Bismuth subcarbonate

The following references support the efficacy of the reformulated product:

***Federal Register* Vol. 51, 161-38-49, No. 83 (4/30/86)**

***Federal Register* Vol. 35, 11707, No. 141 (7/22/70)**

Dekker, W. and K. Reisma, Treatment of Duodenal Ulcers with Bismuth, *Annals of Clinical Research,* Vol. 11, pp. 94-97, 1979.

V. TARGET ANIMAL SAFETY

Kanamycin sulfate

Orally administered kanamycin sulfate is generally considered to be poorly absorbed systemically through intact intestinal mucosa, although the possibility of increased absorption through ulcerated or denuded areas should be considered especially when the dose is increased.

Dogs, particularly those weighing less than 5 pounds, should be observed for systemic nephrotoxic and ototoxic side effects due to systemic absorption of kanamycin sulfate from ulcerated areas following oral administration. Since orally administered kanamycin sulfate is

not expected to reach therapeutic levels, Amforol should not be prescribed for treating Salmonella septicemia. A "Contraindication" appears on the labeling as follows:

"Amforol is contraindicated in treatment of Salmonella septicemias."

Bismuth subcarbonate

Orally administered bismuth subcarbonate is an insoluble salt and generally not absorbed in significant amounts. There is documentation of systemic absorption from an ulcerated gastrointestinal tract.

Systemically available bismuth has been associated with hepatopathy, nephropathy and neurotoxicity in humans. The neurotoxic syndrome has been characterized by lack of energy, muscle twitching, confusion, convulsions and coma.

Winship, K. A."Toxicity of Bismuth Salts" Adv. Drug React. Ac. Pois. Rev. 2 1983 103-121.

Hoffman, R. S. et al "Bismuth Absorption and Myotonic Encephalopathies After Bismuth Subsalicylate Therapy" Vet Hum Toxicol 31 (4) Aug. 1989.

An adverse reaction reported central nervous system disfunction in two dogs after use of Amforol Suspension at the recommended dose.

The "Side Effects" section of the labeling includes:

"The bismuth subcarbonate in Amforol (Veterinary Oral Tablets) may produce darkening of the tongue and stools which can be confused with melena. Prolonged exposure to orally administered bismuth salts has been associated with encephalopathies in other species. Signs may include lack of energy, muscle twitching, confusion, convulsions and comas."

Activated attapulgite (aluminum magnesium silicate) and pectin when orally administered have not been reported to produce toxicity.

See the original FOI for additional information

VI. AGENCY CONCLUSIONS

Removal of aminopentamide increases the safety of Amforol. The reformulation is supported by substantial evidence of safety and effectiveness as found in the veterinary and human medical literature. The effectivenss of the reformulated product is also based on data in the original approval human monographs for antidiarrheal products and NAS/NRC reviews.

The data meet the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. The data demostrate that the product when used according to the approved labeling is safe and effective for the treatment of bacterial enteritis caused by suspectible strains of *E. coli, Salmonella, Shigella, Alcaligenes faecalis, Proteus spp.* and *Staphylococcus aureus.*

This product must be dispensed under a prescription because the expertise of a veterinarian is necessary for the diagnosis of etiologies causing enteritis. A veterinarian's expertise is also needed to monitor response to treatment and to detect and treat adverse reactions if they occur.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(c)(2)(F)(iii), this change in the drug product does not qualify for exclusivity because new clinical or field investigations were not required for approval.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.