FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-419

COYDEN 25 and FLAVOMYCIN

Clopidol and Bambermycins

Type A Medicated Articles to be used in the Manufacture of
Type C Medicated Feeds

Broiler Chickens

As an aid in the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti, and E. mivati* and for increased rate of weight gain and improved feed efficiency in broiler chickens.

Sponsored by:

Huvepharma AD
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I. GENERAL INFORMATION:

A. File Number

NADA 141-419

B. Sponsor

Huvepharma AD
5th Floor
3A Nikolay Haytov Str.
1113 Sofia, Bulgaria

Drug Labeler Code: 016592

U.S. Agent: Kelly W. Beers, Ph.D.
525 Westpark Drive
Suite 230
Peachtree City, GA 30269

C. Proprietary Name

COYDEN 25 and FLAVOMYCIN

D. Established Name

Clopidol and bambermycins

E. Pharmacological Category

Clopidol: Anticoccidial
Bambermycins: Antimicrobial

F. Dosage Form:

Type A medicated articles to be used in the manufacture of Type C medicated feeds

G. Amount of Active Ingredient

25% clopidol, 1 to 2 g/lb bambermycins

H. How Supplied

COYDEN 25: 50 lb bag (Type A medicated article); FLAVOMYCIN: 50 lb bag (Type A medicated article)

I. Dispensing Status

OTC
J. Dosage Regimen

1) Feed 113.5 g clopidol and 1 to 2 g bambermycins per ton of feed continuously as the sole ration up to 16 weeks of age as an aid in the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. mivati* and for increased rate of weight gain and improved feed efficiency.

2) Feed 227 g clopidol and 1 to 2 g bambermycins per ton of feed continuously as the sole ration until 5 days before slaughter up to 16 weeks of age as an aid in the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. mivati* and for increased rate of weight gain and improved feed efficiency. Withdraw 5 days before slaughter or feed 113.5 g per ton clopidol and 1 to 2 g bambermycins per ton of feed during those five days before slaughter.

K. Route of Administration

Oral, in feed

L. Species/Class

Chickens, broilers

M. Indication

As an aid in prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. mivati* and for increased rate of weight gain and improved feed efficiency in broiler chickens.

II. EFFECTIVENESS:

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act (ADAA) of 1996, if the animal drugs or active ingredients intended for use in combination in an animal feed have already been separately approved for the particular uses and conditions for which they are intended for use in combination, the Center for Veterinary Medicine (CVM) will not refuse to approve an NADA for the combination on effectiveness grounds unless the FDA finds that the sponsor fails to demonstrate that:

- there is substantial evidence to indicate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the proposed combination makes a contribution to the labeled effectiveness
- each of the active ingredients or animal drugs intended for at least one use that is different from all other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target population
- where the combination contains more than one nontopical antibacterial active ingredient or animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness.
Clopidol, as provided by Huvepharma AD, has previously been separately approved for use in feed for broiler chickens as an aid in the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. mivati* (21 CFR 558.175(d)(1) and (d)(8)). Bambermycins, as provided by Huvepharma AD, has previously been separately approved for use in feed for broiler chickens for increased rate of weight gain and improved feed efficiency (21 CFR 558.95(d)(1)(i)). Effectiveness of each drug, clopidol and bambermycins, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Huvepharma’s approved NADAs 034-393 and 044-759 for clopidol and bambermycins, respectively.

Because clopidol and bambermycins each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that clopidol and bambermycins provide appropriate concurrent use for the intended target population. The use of clopidol and bambermycins provides appropriate concurrent use because these drugs are intended to treat different conditions (coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. mivati* and for increased rate of weight gain and improved feed efficiency) likely to occur simultaneously with sufficient frequency in broiler chickens. There is no more than one nontopical antibacterial contained in this combination animal drug intended for use in Type C medicated feed.

**III. TARGET ANIMAL SAFETY:**

In accordance with the FFDCA, as amended by the ADAA of 1996, if the animal drugs or active ingredients intended for use in combination in animal feed have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, CVM will not refuse to approve an NADA for the combination on target animal safety grounds unless:

- there is a substantiated scientific issue specific to an active ingredient or animal drug used in the combination that cannot adequately be evaluated based on the information contained in the application for the combination, and CVM finds that the application fails to show that the combination is safe, or
- there is a scientific issue raised by target animal observations contained in the studies submitted to the NADA for the combination, and CVM finds that the application fails to show that the combination is safe.

Clopidol, as provided by Huvepharma AD, has previously been separately approved for use in feed for broiler chickens as an aid in the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. mivati* (21 CFR 558.175(d)(1) and (d)(8)). Bambermycins, as provided by Huvepharma AD, has previously been separately approved for use in feed for broiler chickens for increased rate of weight gain and improved feed efficiency (21 CFR 558.95(d)(1)(i)).

Under the provisions of ADAA, this original approval allows for the combination of clopidol (as provided by Huvepharma AD) and bambermycins (as provided by Huvepharma AD). Target animal safety for each drug, clopidol and
bambermycins, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Huvepharma’s approved NADAs 034-393 and 044-759 for clopidol and bambermycins, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of clopidol and bambermycins when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of the NADA for this combination. Therefore, in accordance with the FFDCA, as amended by the ADAA of 1996, no specific target animal safety studies are required for approval of this application.

IV. HUMAN FOOD SAFETY:

In accordance with the FFDCA, as amended by the ADAA of 1996, if the animal drugs or active ingredients intended for use in combination in animal feed have already been separately approved for the particular uses and conditions of use for which they are intended for use in combination, CVM will not refuse to approve an NADA for the combination on human food safety grounds unless CVM finds that the application fails to establish that:

- none of the active ingredients or animal drugs used in combination at the longest withdrawal for any of the active ingredients or animal drugs in the combination exceeds the established tolerance, or
- none of the active ingredients or animal drugs in combination interferes with the method of analysis for another active ingredient or animal drug in the combination.

A. Toxicology:

CVM did not require toxicology studies for this approval. Safety of the individual drugs in this combination drug have been established by data in NADA 034-393 for clopidol (33 FR 17627, dated November 26, 1968), and NADA 044-759 for bambermycins (FOI Summary dated September 21, 1993).

B. Residue Chemistry:

1. Summary of Residue Chemistry Studies

a. Total Residue and Metabolism Study

CVM did not require total residue and metabolism studies for this approval. NADA 034-393 contains summaries of studies supporting the approval of clopidol in broiler chickens (33 FR 17627, dated November 26, 1968; 37 FR 13531, July 11, 1972). NADA 044-759 (38 FR 1274, dated January 11, 1973) contains summaries of the studies supporting the approval of bambermycins in broiler chickens.

b. Comparative Metabolism Study

CVM did not require comparative metabolism studies for this approval. NADA 034-393 contains summaries of studies supporting the approval of clopidol in broiler chickens (33 FR 17627, dated November 26, 1968; 37 FR 13531, July 11, 1972). NADA 044-759 (38 FR 1274, dated
January 11, 1973) contains summaries of the studies supporting the approval of bambermycins in broiler chickens.

c. Tissue Residue Depletion Study

CVM did not require tissue residue depletion studies for this approval. Data from the previous approvals for clopidol (NADA 034-393) and bambermycins (NADA 044-759) were used to support a white paper addressing assay noninterference and residues resulting from the combination use of clopidol plus bambermycins.

Bambermycins are poorly absorbed and, therefore, are unlikely to interfere with the analysis of clopidol residues in tissues. Bambermycins are approved with zero withdrawal and no tolerances are assigned.

In the previously conducted residue depletion study, clopidol residues at zero withdrawal in broiler chickens treated with clopidol plus bambermycins were significantly below the codified tolerances for clopidol, 15 ppm in liver and 5 ppm in muscle.

Table 1. Clopidol residues, at zero day withdrawal, in tissues of broiler chickens fed feeds containing clopidol and bambermycins.

<table>
<thead>
<tr>
<th>Dietary Treatments</th>
<th>Sex of birds</th>
<th>Concentration of Clopidol in Skin with fat (ppm)*</th>
<th>Concentration of Clopidol in Muscle (ppm)*</th>
<th>Concentration of Clopidol in Kidney (ppm)*</th>
<th>Concentration of Clopidol in Liver (ppm)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No medication</td>
<td>Female</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No medication</td>
<td>Male</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bambermycins 50 ppm plus Clopidol 125 ppm</td>
<td>Female</td>
<td>0.36</td>
<td>1.56</td>
<td>3.125</td>
<td>5.35</td>
</tr>
<tr>
<td>Bambermycins 50 ppm plus Clopidol 125 ppm</td>
<td>Male</td>
<td>0.98</td>
<td>2.5</td>
<td>3.3</td>
<td>5.3</td>
</tr>
</tbody>
</table>

* The concentration reported is the highest tissue concentration quantitated in any bird.

Based on these study data, residues of clopidol following treatment with 227 g/ton clopidol in combination with bambermycins continuously for the entire feeding period with a range of 1 to 2 g/ton, would be expected to be below the clopidol tolerances following a 5-day withdrawal. The 5-day withdrawal period applies to feeding both clopidol and bambermycins.

Also based on these study data, residues of clopidol following treatment with 227 g/ton clopidol followed by clopidol at 113.5 g/ton feed for the last five days prior to slaughter in combination with bambermycins continuously for the entire feeding period with a range of 1 to 2 g/ton, are expected to be below the clopidol tolerances at zero withdrawal. The zero withdrawal period applies to feeding both clopidol and bambermycins.
2. Target Tissue and Marker Residue Assignment

No reassessments of target tissue and marker residue were needed for this approval. A target tissue is not codified for clopidol. The marker residue for clopidol is clopidol (3,5-dichloro-2,6-dimethyl-4-pyridinol). Neither a target tissue nor a marker residue is codified for bambermycins.

3. Tolerance Assignments

The tolerances for residues of clopidol (3,5-dichloro-2,6-dimethyl-4-pyridinol) in broiler chickens are 15 ppm in liver and kidney and 5 ppm in muscle.

A tolerance is not required for bambermycins.

4. Withdrawal Time

A zero day withdrawal is assigned for broiler chickens treated with clopidol at 113.5 g/ton feed plus bambermycins continuously for the entire feeding period with a range of 1 to 2 g/ton.

A zero day withdrawal is assigned for broiler chickens treated with clopidol at 227 g/ton feed followed by clopidol at 113.5 g/ton feed for five days prior to slaughter plus bambermycins continuously for the entire feeding period with a range of 1 to 2 g/ton. The zero day withdrawal period applies to feeding both clopidol and bambermycins.

A 5-day withdrawal is assigned for broiler chickens treated with clopidol at 227 g/ton, in combination with bambermycins continuously for the entire feeding period with a range of 1 to 2 g/ton. The 5-day withdrawal period applies to feeding both clopidol and bambermycins.

C. Microbial Food Safety:

With respect to the human food safety evaluation for these types of combination new animal drug approvals, the agency is permitted only to evaluate whether any active ingredient or drug intended for use in the combination exceeds its established tolerance at the longest withdrawal time of any of the active ingredients or drugs in the combination, and whether any of the active ingredients or drugs of the combination interferes with the methods of analysis of another active ingredient or drug in the combination (section 512(d)(4)(A) of the Federal Food, Drug, and Cosmetic Act). Therefore, we did not 1) assess the impact of this combination of clopidol and bambermycins on antimicrobial resistance among bacteria of public health concern in or on treated broiler chickens, or 2) assess the impact of residues of clopidol and bambermycins in edible food products from treated broiler chickens on human intestinal flora, or need to establish a microbiological acceptable daily intake.
D. Analytical Method for Residues:

1. Determinative Method

A high performance liquid chromatography (HPLC) with ultraviolet detection (UV) analytical method adequate for quantitating residues of clopidol exists (AOAC Official Method 2003.04). A regulatory analytical method for bambermycins is not required because of the establishment of a zero day withdrawal period. However, a microbiological assay method adequate for quantitating residues of bambermycins is available.

2. Availability of Method

The method is on file with the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to the Type C medicated feed:

There are no user safety concerns.

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 contained in the previously approved NADAs for COYDEN 25 and FLAVOMYCIN demonstrate that, when they are used according to the label, they are safe and effective as an aid in the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. mivati* and for increased rate of weight gain and improved feed efficiency. Additionally, data demonstrate that residues in food products derived from broiler chickens treated with COYDEN 25 and FLAVOMYCIN will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

This product can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

B. Exclusivity:

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act.

C. Patent Information:

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