Approval Date: March 8, 2001

# FREEDOM OF INFORMATION SUMMARY

# ORIGINAL NEW ANIMAL DRUG APPLICATION

# NADA 140-942

**Narasin and Nicarbazin (MAXIBAN®) plus Bambermycins (FLAVOMYCIN®)**

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

**Sponsored by:**

**Elanco Animal Health**
**A Division of Eli Lilly & Co.**
**Lilly Corporate Center**
**Indianapolis, IN 46285**

# FREEDOM OF INFORMATION SUMMARY

## Combined use of MAXIBAN® and FLAVOMYCIN® in Broiler Chicken Feeds

## I. GENERAL INFORMATION

**NADA:** 140-942

**Sponsor:** Elanco Animal Health
A Division of Eli Lilly & Co.
Lilly Corporate Center
Indianapolis, IN 46285

**Generic Names:** Narasin/Nicarbazin
Bambermycins

**Trade Names:** MAXIBAN®
FLAVOMYCIN®

**Marketing Status:** OTC

## II. INDICATIONS FOR USE

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

## III. DOSAGE

A. Dosage form: This NADA provides for the combined use of these two Type A medicated articles: narasin/nicarbazin as per 21 CFR 558.363 (d)(1)(iii)and 558.366 (c), and bambermycins as per 21 CFR 558.95 (d)(1)(i). Narasin/nicarbazin are supplied as a Type A medicated article in a concentration of 36 grams each of narasin and nicarbazin activity per pound (fixed 1:1 ratio). Bambermycins is supplied as a Type A medicated article in concentrations of 2, 4, or 10 grams bambermycins activity per pound.

(**Note:** Narasin/nicarbazin will hereafter be referred to as Maxiban®, the Type A medicated article containing a fixed 1:1 ratio of narasin and nicarbazin)

B. Route of Administration: Oral, via the feed.

C. Recommended Dosage:

| | |
|---|---|
| Maxiban® | Narasin and nicarbazin in Maxiban® are added to broiler chicken feed at a rate to provide concentrations of each at 27 to 45 g/ton for the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati,* and *E. maxima*. |
| Bambermycins | Bambermycins is added to broiler chicken feed at concentrations from 1 to 2 g/ton for increased rate of weight gain and improved feed efficiency. |

**WARNING:** Withdraw five (5) days prior to slaughter.

**CAUTION:** For broiler chickens only. Nicarbazin medicated broiler chickens may show reduced heat tolerance when exposed to high temperature and high ambient humidity. Provide adequate drinking water and ventilation during these periods. Do not allow adult turkeys, horses, or other equines access to formulations containing narasin. Ingestion of narasin by these animals has been fatal. Do not feed to laying hens.

## IV. EFFECTIVENESS

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs 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, FDA will not refuse to approve an NADA for the combination on effectiveness grounds unless the Agency finds that the NADA fails to demonstrate that 1) there is substantial evidence to demonstrate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the combination makes a contribution to the labeled effectiveness, 2) 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, or 3) 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 (21 USC 360b (d)(4)(D)).

MAXIBAN®, as provided by Elanco Animal Health, Inc., has previously been separately approved for use in broiler chicken feed for the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati,* and *E. maxima* coccidiosis (21 CFR 558.363 (d)(1)(iii) and 558.366 (c)). Bambermycins, as provided by Intervet, has previously been separately approved for use in broiler chicken feed for increased rate of

weight gain and improved feed efficiency (21 CFR 558.95 (d)(1)(i)). Effectiveness for each drug, Maxiban® and bambermycins, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health's approved NADA 138-952, and in Intervet's approved NADA 44-759, to which Elanco has right of reference, respectively. Because Maxiban® 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 Maxiban® plus bambermycins provides appropriate concurrent use for the intended target population. The use of Maxiban® plus bambermycins provides appropriate concurrent use because these drugs are intended to treat different conditions (Maxiban®, coccidiosis; bambermycins, performance) likely to occur simultaneously with sufficient frequency in broiler chickens. There is no more than one nontopical antibacterial (bambermycins) contained in this combination animal drug intended for use in Type C medicated feed. Maxiban® is not considered to be an antibacterial animal drug for use in broiler chickens for the purposes of §512 (d)(4) of the FFDCA, because Maxiban® is approved only for prevention of a protozoal disease in broiler chickens.

## V. ANIMAL SAFETY

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the active ingredients have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA 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 or a scientific issue is raised by target animal observations contained in studies submitted to the NADA for the combination and FDA finds that the application fails to establish that such combination active ingredient or animal drug is safe for the target animal.

Maxiban®, as provided by Elanco Animal Health, has previously been separately approved for use in broiler chicken feed for the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati,* and *E. maxima,* (21 CFR 558.363 (d)(1)(iii) and 558.366 (c)). Bambermycins, as provided by Intervet, has previously been separately approved for use in broiler chicken feed for increased rate of weight gain and improved feed efficiency (21 CFR 558.95 (d)(1)(i)). Target animal safety for each drug, Maxiban® and bambermycins, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health's approved NADA 118-980 and 135-468, respectively, and in Intervet's approved NADA 44-759, to which Elanco Animal Health has a right of reference, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of Maxiban® or 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. Thus, pursuant to FFDCA, as amended by the Animal Drug Availability Act of 1996, no specific target animal safety study is required for approval of NADA 140-942.

## VI. HUMAN SAFETY

A. Toxicity Studies and Tolerances

The basic safety study for narasin and nicarbazin may be found in parent NADA 138-952 (Maxiban® for Chickens) and for bambermycins in NADA 44-759. A tolerance of 480 ppb is established for parent narasin in abdominal fat of chickens. For nicarbazin, the tolerance of 4 ppm is established for the residues of nicarbazin in uncooked chicken muscle, liver, skin, and kidney. Tolerances for bambermycins are not required.

B. Residue and Assay Noninterference Studies

A tissue residue study (AAC8807) was conducted to demonstrate that there is no change in the residue depletion pattern for narasin and nicarbazin when fed to broiler chickens in combination with bambermycins. There were two segments to the study: (1) validation of the assay by assaying spiked tissue samples with the cited drugs, and (2) assays for narasin and nicarbazin conducted on tissue samples harvested from medicated birds. Control samples fortified with narasin (0.2 ppm), nicarbazin (4.0 ppm) and bambermycins (0.1 ppm) demonstrated that no interference was observed with the assay of narasin or nicarbazin in their respective target tissues in the presence of bambermycins.

Four male and female broiler chickens medicated with Flavomycin® (4 g/ton) and Maxiban® (100 g/ton) for 49 days until slaughter 6 hours (practical zero) or 1, 2, or 4 days following medicated feed withdrawal. The mean residue level of narasin in the practical zero withdrawal (6-hour) abdominal fat tissue was determined to be 0.055 ppm. There were no detectable narasin residues found in the 2 and 4-day withdrawal abdominal fat tissues at a test sensitivity of 0.02 ppm.

The mean residue levels of nicarbazin in liver were 6.2 ppm at practical zero withdrawal (6 hours), 2.0 ppm at 1 day of withdrawal, 0.3 ppm at two days of withdrawal, and < 0.1 ppm at 4 days of withdrawal. A statistical analysis of the data for nicarbazin using CVM's 99% tolerance limit with 95% confidence procedure supported the assignment of a 5-day withdrawal period for the subject combination.

Substantial scientific information provided by Hoechst Roussel Vet shows that the likelihood of other drugs in combination with bambermycins altering the bambermycins residues in tissues of animals is extremely improbable; there are no longer requirements for conducting studies demonstrating tissue residue and analytical method non-interference for Hoechst Roussel Vet's bambermycins where it is included at already approved levels. Such is the case for this combination. Data generated over many years show that residues of bambermycins are not detected, whether the drug is used alone or in combination.

## VII. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of Section 512 of the FFDCA and demonstrate that Maxiban® (narasin and nicarbazin in a ration of 1:1, 27 to 45 g/ton) plus bambermycins (1 to 2 g/ton) with a 5-day withdrawal period are safe and effective for the claims indicated in Section II of this FOI summary.

Pursuant to 21 CFR 514.106 (b)(2)(vi), this combination NADA approval is regarded as a Category II supplemental change which did not require a reevaluation of safety and efficacy data in the parent NADAs. The drugs are to be fed in Type C medicated feeds, in accordance with Section II and III of the FOI Summary and the Blue Bird labeling that is attached to this document.

Attached labeling: Type C medicated feed (Blue Bird).

Net weight lb (kg) on bag or bulk

# Narasin and Nicarbazin/Bambermycins Broiler Chicken Ration
## Type C Medicated Feed

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

### Active Drug Ingredient

Narasin……27 to 45 g/ton
Nicarbazin……27 to 45 g/ton
Bambermycins……1.0 to 2.0 g/ton

### Guaranteed Analysis

Crude Protein, not less than……_____%
Lysine, not less than……_____%
Methionine, not less than……_____%
Crude Fat, not less than……_____%
Crude Fiber, not more than……_____%
Calcium, not less than……_____%
Calcium, not more than……_____%
Phosphorus, not less than……_____%
Salt[1], not less than……_____%
Salt[1], not more than……_____%
Sodium[2], not less than……_____%
Sodium[2], not more than……_____%

[1]If added.
[2]Shall be guaranteed only when total sodium exceeds that furnished by the maximum salt guarantee.

### Ingredients

Each ingredient must be named in accordance with the names and definitions adopted by the Association of American Feed Control Officials.

### Directions for Use

Feed continuously as sole ration. Narasin and nicarbazin can be combined only at a 1:1 ratio for the 27 to 45 g/ton range.

**WARNING:** Withdraw five (5) days prior to slaughter.

(OVER)

**CAUTION:** For broiler chickens only. Nicarbazin medicated broiler chickens may show reduced heat tolerance when exposed to high temperature and high ambient humidity. Provide adequate drinking water and ventilation during these periods. Do not allow adult turkeys, horses, or other equines access to formulations containing narasin. Ingestion of narasin by these animals has been fatal. Do not feed to laying hens.

**MANUFACTURED BY**

BLUE BIRD FEED MILL
Anytown, USA 12345