Date: 5/11/2016

FREEDOM OF INFORMATION SUMMARY

IMPORT TOLERANCE

I. GENERAL INFORMATION

A. Established Name: lufenuron

B. Food-Animal Species: salmonids

C. Tolerances/tissues: 1.35 ppm lufenuron in salmonids muscle/skin

D. File Number: VMF 006-081

E. Petitioner: Novartis Animal Health US, Inc.

II. HUMAN FOOD SAFETY

A. Microbial Food Safety:

1. Antimicrobial Resistance:

The Agency determined there is no need to develop, or submit for review, any microbial food safety (antimicrobial resistance) information regarding this proposed use of lufenuron in salmonids as it relates to its import tolerance.

2. Impact of Residues on Human Intestinal Flora:

At this time, the Agency thinks that lufenuron is not an antimicrobial drug and has no activity against bacteria. Its residues and/or metabolites are not expected to impact human intestinal flora; therefore, there is no need to determine a microbiological ADI at the consideration of establishing an import tolerance for the compound. The final ADI should be derived from the toxicological ADI.

B. Toxicology:

Toxicity tests determining the human food safety of lufenuron are summarized below:

1. Summary of Toxicology Studies:

Study Type	Description
Sub-Chronic Oral Toxicity in Rodents:	3-Month Oral Toxicity Study in Rats (Administration in Food) (Study 871736)
Sub-Chronic Oral Toxicity Study in Non-Rodents:	3-Month Range Finding Toxicity Study in Mice (Administration in Food) (Study 891029)
Sub-Chronic Oral Toxicity Study in Non-Rodents:	13-week Subchronic Dietary Toxicity Study in Beagle Dogs (Study 881141)

Study Type	Description
Chronic Oral Toxicity Study in Non-Rodents:	12-Month Chronic Dietary Toxicity Study in Beagle Dogs (Study 932039)
Oral Pre-Natal Developmental Toxicity Study in Rodents:	Oral Pre-Natal Developmental Toxicity Study of Lufenuron in Rats (Study F-00015)
Oral Pre-Natal Developmental Toxicity Study in Non-Rodents:	Oral Pre-Natal Developmental Toxicity Study of Lufenuron in New Zealand White Rabbits (Study F-00033)
Two-Generation Oral Reproductive Toxicity Study in Rodents:	Two-Generation Dietary Reproduction Study with lufenuron in Rats (Study 881047)
Chronic Oral Toxicity Study in Rodents:	24-Months Carcinogenicity and Chronic Toxicity Study with lufenuron in Rats (Study 881125)
Oral Carcinogenicity Study in Rodents:	18-Month Carcinogenicity Study with lufenuron in Mice (Study 881124)
Oral Neurotoxicity Study in Rodents	4-Month Oral Subchronic Neurotoxicity Study with lufenuron in Male Rats (Study 911026)

Genetic Toxicology Studies:

- Bacterial Reverse Mutation Assay (Ames Test): Two *Salmonella*/Mammalian Microsome Mutagenicity tests (Study 871717 and 871455)
- Bacterial Reverse Mutation Assay (Ames Test): One *Salmonella* and *Escherichia*/Liver Microsome test (Study 901121)
- Gene Mutation Test: *In vitro* Point Mutation Test with Chinese Hamster Cell V79 (Study 871719)
- Gene Mutation Test: *In vitro* Mammalian Cell Gene Mutation Test with Chinese Hamster Cell V79 (Study 982006)
- Mammalian Erythrocyte Micronucleus Test: Micronucleus Test in Mouse (Study 871714)
- Unscheduled DNA synthesis test: Autoradiographic DNA Repair Test on Rat Hepatocytes *in vitro* (Study 871715)
- Unscheduled DNA synthesis test: Autoradiographic DNA Repair Test on Human Fibroblasts (Study 871716)
- Unscheduled DNA synthesis test: Unscheduled DNA Synthesis Test of CGA184699 in Cultured Human Cells (Study G-96-061)
- *In vitro* Chromosome aberration test: Two Chromosome Studies on Chinese Hamster Ovary Cell Line CCL 61 *in vitro* (Study 871718 and 881372)
- Unscheduled DNA synthesis test: Two *In vivo*/*In vitro* Unscheduled DNA Synthesis Studies in Rat Hepatocytes (Study 932124 and 992048)
- *In vitro* Mammalian Chromosome Aberration test: Cytogenetic Test on Chinese Hamster Cells *in vitro* (Study 901122)

Non-Pivotal Studies:

- 4-Week Oral Dose Range Finding Study
- 90-Day Toxicity Study in Rats
- 90-Day Toxicity Study in Mice

2. Determination of No Observed Effect Level (NOEL) for chronic exposure:

Based on the available toxicology studies, the NOEL/NOAEL of 1.5 mg/kg bw/day from a 52-week oral toxicity study in dogs (Study Number 932039) was selected to be the most appropriate study for the determination of the toxicological ADI for chronic exposure of total residues of lufenuron to human consumers.

3. Acceptable Daily Intake (ADI):

With lack of antibacterial activity for lufenuron, a microbiological ADI was not needed. Therefore, the toxicological ADI was set as the final ADI. The toxicological ADI for total residues of lufenuron is calculated using the following formula based on the

NOEL/NOAEL of 1.5 mg/kg bw/day from the 52-week oral toxicity study in dogs and a safety factor of 100. A safety factor of 100 was applied to account for a 10-fold factor for animal-to-human variability and a 10-fold factor for human to human variability.

$$\text{Toxicological ADI} = \frac{\text{NOEL/NOAEL}}{\text{Safety Factor}} = \frac{1.5\ \text{mg/kg bw/day}}{100}$$

$$= 0.015\ \text{mg/kg bw/day} = 15\ \mu\text{g/kg bw/day}$$

The toxicological ADI for lufenuron is 15 µg/kg bw/day.

4. Safe Concentrations for Total Residues (edible tissues and injection sites, if applicable):

The calculation of the tissue safe concentrations is based on the General Principles for Evaluating the Safety of Compounds used in Food-Producing Animals (FDA/CVM, revised July 2006). The daily consumption value of the edible tissue of fish (muscle and skin in natural proportion) is approximated as 300 g. The safe concentration of total lufenuron residues (ppm) in the edible tissue of fish (muscle with adhering skin in natural proportion) is calculated as the following:

$$\text{Safe Concentration} = \frac{\text{ADI} \times \text{Human Body Weight}}{\text{Food Consumption Value}}$$

$$= \frac{15\ \mu\text{g/kg bw/day} \times 60\ \text{kg}}{300\ \text{g/day}} = 30\ \mu\text{g/g} = 3\ \text{ppm}$$

Therefore, the safe concentration for total lufenuron residues is 3 ppm in fish muscle with adhering skin in natural proportions.

C. Summary of Residue Chemistry Studies:

1. Total Residue and Metabolism Studies:

The Metabolism, Excretion and Residue Depletion of [^{14}C]-Lufenuron in the Atlantic salmon (*Salmo salar* L.) (Study 811438).

Uptake, depuration and bioconcentration of ^{14}C-CGA 184699 by bluegill sunfish (*Lepomis macrochirus*) (Study 34914).

Characterization of ^{14}C-CGA 184699 in bluegill sunfish (*Lepomis macrochirus*) (Study 35426).

Lufenuron: Determination of the accumulation and elimination of [^{14}C] lufenuron in fathead minnow (*Pimephales promelas*) (Study 03-0057-D Report No. BL7791/B with PROTOCOL 03-0057-D).

Data from total residue and metabolism studies in three fish species indicate that lufenuron is not extensively metabolized. Parent lufenuron is the major component of total residues in fish muscle/skin.

2. Comparative Metabolism Studies:

Absorption, distribution, metabolism and excretion of [U-^{14}C] dichlorophenyl CGA 184699 in the rat (Project 22/90).

The metabolism of [U-^{14}C] dichlorophenyl CGA 184699 in the rat (Study 43/90).

Bioavailability and balance determination of [^{14}C]-CGA 184699 (lufenuron in dogs (Study CRA 97/071).

The major metabolite of lufenuron in fish is parent drug, which also is present in the rat and in the dog.

3. Target Tissue and Marker Residue Assignment:

The target tissue is muscle with adhering skin. The marker residue is parent drug, lufenuron, because data from the total residue and metabolism study in Atlantic salmon (Study No. 811438) indicate that parent lufenuron is the major component of total residues.

4. Tolerance Assignment:

An import tolerance of 1.35 ppm is established for lufenuron in salmonids.

5. Withdrawal Period:

A withdrawal period is not assigned when establishing an import tolerance.

D. Analytical Method for Residues:

FDA monitors for lufenuron using a multi-residue pesticide monitoring procedure. The LC-MS/MS analytical procedure is described in Laboratory Information Bulletin (LIB) 4463. The LIB is available from the Office of Regulatory Science/Office of Regulatory Affairs/FDA *via* the agency FOI request (http://www.fda.gov/regulatoryinformation/foi/howtomakeafoiarequest/default.htm.

E. Conclusions:

The Center for Veterinary Medicine concludes that we have the appropriate information for us to assign an import tolerance for lufenuron in salmonids. We assign an import tolerance of 1.35 ppm lufenuron in muscle/skin of salmonids.

III. AGENCY CONCLUSIONS

These data support the establishment of an import tolerance of 1.35 ppm lufenuron in muscle/skin of salmonids as provided under Sec. 512(a)(6) of the Food, Drug, and Cosmetic Act.