

CODEX ALIMENTARIUS COMMISSION



Food and Agriculture
Organization of the
United Nations



World Health
Organization

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Agenda Item 11

CX/RVDF 21/25/12-Add.1

June 2021

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

25th Session

(Virtual)

12-16 and 20 July 2021

COMMENTS IN REPLY TO CL 2020/18-RVDF ON PRIORITY LIST OF VETERINARY DRUGS
FOR EVALUATION OR RE-EVALUATION BY
THE JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES (JECFA)

Comments received from Brazil and Norway

Brazil

ANNEX A

TEMPLATE FOR INFORMATION NECESSARY FOR PRIORITIZATION BY CODEX COMMITTEE ON RESIDUES OF
VETERINARY DRUGS IN FOODS

Administrative information

1. Member(s) submitting the request for inclusion

BRAZIL

SINDICATO NACIONAL DA INDÚSTRIA DE PRODUTOS PARA SAÚDE ANIMAL – SINDAN – *Brazilian Animal Health Products Industry Association* (coordination)

Sponsors: BOEHRINGER INGELHEIM (responsible for submission); CEVA SAÚDE ANIMAL; UNIÃO QUÍMICA FARMACÊUTICA NACIONAL S/A

2. Veterinary drug names

Fipronil

3. Trade names

CEVA: CP012 (project code) – new submission

COMBATT 3

TOPLINE POUR-ON

TOPLINE SPRAY

4. Chemical names and CAS registry number

International Non-proprietary Name (INN): *fipronil*

Synonyms: *MB 46030*

Chemical abstract service N^o: *120068-37-3*

IUPAC Name: *(±) - 5-amino-1- (2,6-dichloro- α , α , α -trifluoro-p-tolyl) -4-trifluoromethyl-sulfinylpyrazole-3-carbonitrile*

5. Names and addresses of basic producers

Holder: CEVA GROUP (SESPO INDÚSTRIA E COMÉRCIO)

Manoel Joaquim Filho Street 303, Paulínia city/ São Paulo state

Manufactured by IPANEMA INDÚSTRIA E COMÉRCIO

Rodovia Raposo Tavares, km 113 - Araçoiaba da Serra city – São Paulo state

Holder: União Química Farmacêutica Nacional S/A

Rua Coronel Tenório de Brito, nº 90 – Centro – Embu Guaçu city – São Paulo state

Manufactured by IPANEMA INDÚSTRIS E COMÉRCIO

Rodovia Raposo Tavares, Km 113 – Araçoiaba da Serra – São Paulo

Holder: Boehringer Ingelheim Animal Health do Brasil Ltda

Fazenda São Francisco, S/N, Paulínia city, Sao Paulo state, ZIP CODE: 13140-970

Manufactured by IPANEMA INDÚSTRIS E COMÉRCIO

Rodovia Raposo Tavares, Km 113 – Araçoiaba da Serra city – São Paulo state

Purpose, scope and rationale

6. Identification of the food safety issue (residue hazard)

The toxicity of fipronil was evaluated by FAO/WHO JMPR in 1997. In that Meeting fipronil and their metabolites in mammals and photodegradation products were considered. An ADI of 0-0.0002 mg/kg bw was established on the basis of a NOAEL of 0.019 mg/kg bw per day in a 2-year study of toxicity and carcinogenicity in rats and a safety factor of 100. Residues of fipronil were assessed by the FAO/JMPR in 2001 and the Committee estimated MRLs and STMR values and limit the residue definition for animal tissues to the sum of fipronil and its sulfone metabolite expressed as fipronil.

The toxicological profile of fipronil as pesticide was evaluated by EFSA in the framework of Directive 91/414/EEC. An ADI of 0.0002 mg/kg bw per day and an ARfD of 0.009 mg/kg bw per day was established.

Fipronil is used in some countries, including Brazil, as pesticide and veterinary drug.

Fipronil was not evaluated by JECFA as veterinary drug and there are no recommended MRLs available for cattle tissues.

7. Assessment against the criteria for the inclusion on the priority list

Fipronil is available as a commercial product and has the potential to cause public health and international trade problems.

A Member has established good veterinary practices with regard to fipronil for use in cattle.

There are relevant data available of toxicology, metabolism, pharmacokinetics and residue depletion in the target species and a dossier will be made available for the risk assessment.

Risk profile elements

8. Justification for use

*Fipronil is a broad-spectrum insecticide widely used to control various pests in crops and as veterinary drug in food producing animals for the control of ectoparasites. Ectoparasite infections represents a serious health problem in cattle. In particular, infestation of *Rhipicephalus (Boophilus) microplus* poses a major obstacle to animal productivity in tropical and sub-tropical areas where this species is endemic, which causes losses and consequently is of economic concern. It is also important to highlight that fipronil is used against ivermectin-resistant strains of *Rhipicephalus (Boophilus) microplus*.*

9. Veterinary use pattern, including information on approved uses if available

Fipronil is a pyrazole insecticide used in veterinary medicine to control ectoparasites in bovine, ovine, caprine and companion animals (dogs and cats). It was discovered and developed by Rhône Poulenc between 1985 and 1987 and released to the market in 1993. Fipronil act disrupting the insect central nervous system via interference with the passage of chloride ions through the GABA regulated chloride channel.

*In Brazil, there are two formulations of fipronil registered for use in cattle, one pour-on with indication against ticks (*Rhipicephalus (Boophilus) microplus*), horn fly (*Haematobia irritans*) and berne (*Dermatobia hominis*), and another, spray with indication against myiasis caused by *Cochliomyia hominivorax* (puppies) larvae.*

The concentration of fipronil in the formulations varies from 0.32 to 5% w/v. Fipronil is used in cattle at single dose of 1 to 2 mg/kg bw. Withdrawal periods range from 10 to 50 days for spray and 25 to 148 days for the pour-on formulation.

10. Commodities for which Codex MRLs are required

Cattle tissues: muscle, liver, kidney and fat.

Risk assessment needs and questions for the risk assessors

11. Specific request to risk assessors

Fipronil is used as pesticide and veterinary drug. There is a need for the recommendation for MRLs based on chronic intake estimates.

Concerns for fipronil effects on public health have been raised because of the wide range of uses of this pesticide and veterinary drug.

Available information

12. Countries where the veterinary drugs are registered

Fipronil is registered as veterinary drug in Brazil, Argentina and Uruguay, and under registration in other Latin America and South Hemisphere countries.

13. National/Regional MRLs or any other applicable tolerances

In Argentina and Uruguay, the following MRLs for the marker residue (fipronil + fipronil sulfone) in cattle tissues are adopted.

Country	Muscle (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Fat (µg/kg)	Milk (µg/kg)
Argentina SENASA N° 559/2011	500 ^a	20	100	-	20
Uruguay DGDG N° 45/017	5	9	15	60	8

a: mg/kg of fat contained in the whole product.

In Brazil, there are no recommended MRLs for fipronil in cattle tissues.

14. List of data (pharmacology, toxicology, metabolism, residue depletion, analytical methods) available

Available studies	
Pharmacology	Pharmacokinetics in laboratory animals (mice, rat, rabbit and dog) and in food producing animals (poultry and cattle)
Toxicology	Toxicology was evaluated by JMPR in 1997 and the Committee established and ADI and ARfD for fipronil.
Metabolism	Metabolism in laboratory animals (mice, rat, rabbit) Metabolism in food producing animals (poultry, goats and cattle).
Residue depletion	Residue depletion studies with radiolabelled fipronil in cattle (one sponsor). Residue depletion studies with non radiolabelled fipronil in cattle (three different sponsors).
Analytical methods	Validated analytical method available for the determination of fipronil and fipronil sulfone in cattle tissues (muscle, liver, kidney and fat) using LC-MS/MS with a limit of quantitation of 5 µg/kg in the four target tissues.

Timetable

15. Date when data could be submitted to JECFA.

Data package is available and could be submitted to JECFA.

Norway

TEMPLATE FOR INFORMATION NECESSARY FOR PRIORITIZATION BY CCRVDF

ADMINISTRATIVE INFORMATION

1. Member(s) submitting the request for inclusion

Norway

2. Veterinary drug names

Imidacloprid

3. Trade names

Ectosan Vet

4. Chemical names and CAS registry number

Common name: Imidacloprid

IUPAC name: (E)-1-(6-chloro-3-pyridylmethyl)-N-nitroimidazolidin-2 ylideneamine

Chemical abstracts name: 2E)-1-[(6-chloro-3-pyridinyl)methyl]-N-nitro-2-imidazolidinimine

CAS 138261-41-3

5. Names and addresses of basic producers

Marketing Authorisation Holders
Benchmark Animal Health Norway AS
Bradbenken 1
5003 Bergen
Norway

Site of final product manufacture
Animax Ltd
Sheperds Grove Industrial Estate
Stanton
Bury St. Edmonds
Suffolk
IP31 2AR
UK

PURPOSE, SCOPE AND RATIONALE

6. Identification of the food safety issue (residue hazard)

Residues in muscle and skin of finfish

7. Assessment against the criteria for the inclusion on the priority list

- A Member (Norway) has proposed the compound for evaluation

A template for information recommended for consideration in the priority list by Codex Committee on Residues of Veterinary Drugs in Foods has been completed and is provided in this document

- A Member has established good veterinary practices with regard to the compound;

Yes

- The compound has the potential to cause public health and/or international trade problems;

Yes

- The compound is available as a commercial product;

Yes

- There is a commitment that a dossier will be made available.

Yes

RISK PROFILE ELEMENTS

8. Justification for use

Sea lice is one of the greatest global challenges to the salmonid aquaculture. Impacting fish health, fish welfare, wild salmon stocks and is leading to substantial economic loss which is estimated to cost producers more than 1billion USD annually.

Ectosan Vet is a new veterinary medicine for the treatment of pre-adult and adult salmon lice (*Lepeophtheirus salmonis*) infestations on Atlantic salmon (*Salmo salar*) and rainbow trout (*Oncorhynchus mykiss*). It represents a new class of active substances for the treatment of sea lice.

The solution combines a highly effective medicine Ectosan® Vet with CleanTreat®, a water purification system which safely removes the medicine from treatment water before releasing purified water into the sea. The medicine has been rigorously reviewed and approved by all relevant regulatory bodies under the strict guidelines of the European Union.

9. Veterinary use pattern, including information on approved uses if available (*this should include product labels or other evidence of official use authorization*)

The SPC will be sent once finalised. Probably June 4th 2021.

10. Commodities for which Codex MRLs are required

Muscle and skin in natural proportions (filet)

RISK ASSESSMENT NEEDS AND QUESTIONS FOR THE RISK ASSESSORS

11. Specific request to risk assessors

To establish MRL for finfish at CCRVDF.

AVAILABLE INFORMATION11

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12. Countries where the veterinary drugs are registered

Pending in Norway (section to be updated when MA granted)

13. National/Regional MRLs or any other applicable tolerances

EU veterinary MRL of 600 µg/Kg for fin fish- Regulation 2021/621, amending EU regulation 37/2010.

14. List of data (pharmacology, toxicology, metabolism, residue depletion, analytical methods) available (*this should include a list of the data available with the full study titles and whether the compound is also registered as pesticide and, as appropriate, has been evaluated or scheduled for evaluation or re-evaluation by JMPR*)

Please see the attached list of available data, both original studies and publications. The compound has been previously reviewed by JMPR as a pesticide and has pesticide MRLs set in Codex. These published evaluations are in the list of data.

TIMETABLE

15. Date when data could be submitted to JECFA.

July 2021 onwards

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