EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 February 2025
EMA/CVMP/27344/2025
Veterinary Medicines Division

Opinion of the Committee for Veterinary Medicinal Products on the establishment of maximum residue limits

Procedure no: EMEA/V/MRL/004380/EXTN/0002

Name of the substance: Fluralaner (INN)

Basis for the opinion

Pursuant to Article 3 of Regulation (EC) No 470/2009 of 6 May 2009, Farmacologia En Aquacultura Veterinaria FAV S.A. submitted to the European Medicines Agency on 24 April 2024 an application for the extension of maximum residue limits for fluralaner to Salmonidae and other fin fish.

On 12 September 2024 the Committee for Veterinary Medicinal Products adopted a list of questions to be addressed by the applicant. The response to the list of questions was submitted on 31 October 2024.

Recommendation

The Committee, having considered the application and having evaluated the response to the list of questions, recommends the extension of maximum residue limits for fluralaner to Salmonidae. Furthermore, with reference to Article 5 of Regulation (EC) No 470/2009, the Committee recommends the extrapolation of the maximum residue limit for Salmonidae to all fin fish. Therefore, the Committee recommends by consensus the amendment of the entry for fluralaner in table 1 of the Annex to Regulation (EU) No 37/2010 of 22 December 2009 as follows:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Fluralaner	Fluralaner	Poultry	65 µg/kg 650 µg/kg 650 µg/kg 420 µg/kg 1300 µg/kg	Muscle Skin and fat in natural proportions Liver Kidney Eggs	NO ENTRY	Antiparasitic agents/ Agents against ectoparasites
		Fin fish	65 µg/kg	Muscle and skin in natural proportions		

The Norwegian CVMP member agrees with the above-mentioned recommendation of the Committee.

The scientific conclusions of the Committee are presented in the European public MRL assessment report (EPMAR), provided in Annex I of this opinion. The analytical method for monitoring of residues is appended to this opinion.

The present opinion is forwarded to the European Commission and to the applicant together with its appendices.

Annex I

European public MRL assessment report (EPMAR)

Fluralaner (Salmonidae and other fin fish)

Summary of the scientific discussion for the establishment of MRLs

Substance name:	**Fluralaner**
Therapeutic class:	NO ENTRY
Procedure number:	EMEA/V/MRL/004380/EXTN/0002
Applicant:	Farmacologia En Aquacultura Veterinaria FAV S.A.
Target species:	Salmonidae (and other fin fish)
Intended therapeutic indication:	For the treatment of juvenile and adult sea lice
Route(s) of administration:	Oral

1. Introduction

Fluralaner belongs to the isoxazoline class of ectoparasiticides and acts as an inhibitor of ligand-gated chloride channels on gamma-aminobutyric acid ($GABA_A$) and L-glutamate receptors. As such, it induces a spastic paralysis of susceptible parasites. Fluralaner is currently used in veterinary medicinal products indicated for the treatment of infestations with various ectoparasites in cats, dogs and poultry.

The current evaluation relates to fluralaner, as intended for use in Salmonidae (and other fin fish) for the treatment of juvenile and adult sea lice. Fluralaner would be used orally in feed at the dose of 0.5 mg per kilogram of fish per day for 7 consecutive days.

Fluralaner was previously assessed by the CVMP and a toxicological ADI of 10 µg/kg bw, i.e. 600 µg/person was established.

Currently, fluralaner is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 in accordance with the following table:

Pharmaco-logically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Fluralaner	Fluralaner	Poultry	65 µg/kg 650 µg/kg 650 µg/kg 420 µg/kg 1300 µg/kg	Muscle Skin and fat in natural proportions Liver Kidney Eggs	NO ENTRY	Antiparasitic agents/ Agents against ectoparasites

2. Scientific risk assessment

2.1. Safety assessment

The CVMP has previously assessed the consumer safety of fluralaner and established an ADI of 10 µg/kg bw, i.e. 600 µg/person, based on the NOEL of 1 mg/kg bw/day determined in a 52-week study in dogs and applying an uncertainty factor of 100 (EMA/CVMP/567262/2016). Therefore, no further assessment regarding the consumer safety of the substance is required for the purpose of this extension application.

2.2. Residues assessment

The parent compound fluralaner is the major component detected in all tissues, as was concluded by CVMP in the European Public MRL Assessment Report (EPMAR) for the establishment of MRLs for fluralaner in poultry. Fluralaner was therefore identified as the marker residue.

Metabolism in fish is considered much simpler than in mammals or poultry. The difference in metabolism in fish is the rate at which it occurs, with metabolism in fish being slower than in mammals, particularly when the temperature of the water of their environment is low (EMA/CVMP/153b/97-final). Consequently, fluralaner is also considered to be the appropriate marker residue in Salmonidae (and other fin fish).

Commission Regulation (EU) 2017/880, laying down rules on the use of a maximum residue limit established for a pharmacologically active substance in a particular foodstuff for another foodstuff derived from the same species and a maximum residue limit established for a pharmacologically active substance in one or more species for other species, in accordance with Regulation (EC) No 470/2009 of the European Parliament and of the Council, provides in Article 6(f) that '*When considering the extrapolation of MRLs between unrelated species and from a minor reference species to a major concerned species, the EMA shall apply the following criteria: extrapolation of MRLs from terrestrial species to fish with muscle and skin in natural proportions is directly possible where the parent compound is the marker residue and MRL has been established in muscle of the reference species'.* The criteria laid down in Article 6(f) of Commission Regulation (EU) 2017/880 were accordingly applied to the present application to extend the MRL value from poultry to Salmonidae, and to the further extrapolation to all fin fish.

Article 4(d) of Commission Regulation (EU) 2017/880 states that a condition for extrapolating MRL values between unrelated species is that "*the similarity of the metabolic profiles in the reference and concerned species is established*". This has not been shown for poultry and fish. However, as metabolism in fish is less complex and less extensive compared to poultry, no change of metabolic profile that would critically affect the marker residue or ratio of marker to total residues is assumed. Therefore, it is acceptable that no metabolism or residue depletion studies have been provided.

2.2.1. Pharmacokinetics in target species

No pharmacokinetic data in target species were submitted - see comments above.

2.2.2. Residue depletion studies

No residue depletion studies were submitted – see comments above.

2.2.3. Monitoring or exposure data

No data on monitoring or exposure data are available. Exposure of the consumer to fluralaner residues would be similar to that already evaluated for poultry.

2.2.4. Analytical method for monitoring of residues

An analytical LC-MS/MS method has been developed and validated for the determination of fluralaner in muscle and skin of Salmonidae in the range of 10 – 200 µg/kg. The method is presented in an internationally recognized format and has been validated in line with the current requirements of Commission Regulation (EU) 2018/782 establishing the methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC) No 470/2009 and with the principles of the VICH GL 49 (EMA/CVMP/VICH/463202/2009).

The current analytical procedure uses commercially available standards, reagents, and equipment. Confirmation is provided that the reference standards used in the proposed bioanalytical method are commercially available. Contact details are included in the certificate provided. Overall, this is aligned with section III.5.3 of Annex I to Commission Regulation (EU) 2018/782.

The results demonstrate that this method is applicable to assessing the levels of fluralaner residues present in muscle and skin of Salmonidae during surveillance programs. The relevant European Reference Laboratory (EURL) has reviewed the analytical method and is in agreement with the above assessment. Although it was not specifically demonstrated, it is expected that the analytical method developed for Salmonidae is basically applicable for other fin fish.

2.2.5. Potential effects on the microorganisms used for industrial food processing

The substance is not intended for use in dairy animals and therefore potential effects in dairy products were not investigated.

2.2.6. Findings of EU or international scientific bodies

Fluralaner has not been evaluated for this purpose by EU or international scientific bodies.

3. Risk management recommendations

Fluralaner in poultry is administered by the oral route. The underlying metabolism and residue depletion studies for the establishment of MRLs in poultry were performed by administration of the substance via the oral route. According to the information provided by the applicant fluralaner will also be administered via the oral route to Salmonidae (and other fin fish).

Fluralaner metabolism appears relatively conserved across species as demonstrated during the MRL procedure for fluralaner in poultry. Moreover, according to EMEA/CVMP/153b/97-FINAL, significant differences between the metabolic profile of substances used in fish and other species are not apparent. Therefore, metabolism in the reference (poultry) and concerned species (Salmonidae and other fin fish) is not expected to be significantly different when applied via the same (oral) route. If applied via another route, for instance topically, and absorbed via skin, metabolism may be different. However, as metabolism in fish is less complex and less extensive compared to poultry, no change of

metabolic profile that would critically affect the marker residue or ratio of marker to total residues would then be assumed.

3.1. Availability of alternative medicines and other legitimate factors

The intended use of fluralaner in Salmonidae (and other fin fish) is 'for the treatment of juvenile and adult sea lice'.

Various VMPs are available for the treatment of sea lice in salmon in the EU. However, due to development of resistance to several of the active ingredients of those products, the availability of new treatment options is considered beneficial.

Technological aspects of food and feed production (potential effects on the microorganisms used for industrial food processing)

In view of the nature of the substance such data are not considered necessary.

Feasibility of controls

Monitoring of residues of fluralaner should focus on muscle tissue with skin.

Other factors that should, if applicable, be taken into consideration for the establishment of maximum residue limits

No other relevant factors were identified.

3.2. Elaboration of MRLs

The principles described in Commission Regulation (EC) No 2017/880 are applied for the evaluation of this application. In line with Article 6(f), extrapolation of an MRL established in terrestrial species can be directly applied to fish muscle and skin in natural proportions where the parent compound is the marker residue and the MRL has been established in muscle of the reference species.

In line with this and given that a suitably validated analytical method has been provided, it is concluded that the MRL established for poultry muscle can be safely extended to muscle with skin of Salmonidae, as shown in the table below.

Tissue	**MRL**
Muscle and skin	65 µg/kg

Calculation of theoretical daily intake of residues

The calculated maximum theoretical daily intake of residues of 360.2 µg, as calculated and described for poultry, remains unchanged as the MRL for muscle and skin of fish will be identical to the MRL for muscle of poultry and also the daily consumption figure is identical (i.e. 0.3 kg muscle in total, irrespective of the source/species). Based on the acceptable daily intake (ADI) of 600 µg fluralaner/person/day and the MRL values proposed, the total theoretical daily intake represents 60% of the ADI.

4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EC) No 470/2009, the CVMP considered the possibility of extrapolating the recommended MRLs as part of its evaluation of the application to establish MRLs in chickens (see EMA/CVMP/576262/2016) and concluded that only extrapolation to poultry could be recommended at that moment. For fin fish it was concluded that 'metabolism in fin fish is generally less complicated than in chickens. Consequently, since the parent compound is the marker residue in chicken it can be assumed that the parent compound would also be the suitable marker residue in fish meat. However, no analytical method for monitoring of residues in fin fish was available for evaluation'.

The additional data made available for the current extension application relate to the analytical method for Salmonidae, for which it was concluded that the analytical method has been successfully validated for the determination of fluralaner in muscle and skin. Due to its design the analytical method developed for Salmonidae is expected to be basically applicable for other fin fish. It is therefore considered justified to extrapolate the recommended MRL in Salmonidae to fin fish.

5. Conclusions and recommendation for the establishment of maximum residue limits

Having considered that:

- the toxicological ADI of 10 µg/kg bw (i.e. 600 µg/person) was established as the overall ADI for fluralaner,
- fluralaner was retained as the marker residue in tissues. Metabolism in fin fish is generally less complicated than in chickens. Consequently, since the parent compound is the marker residue in chicken it can be assumed that the parent compound would also be the suitable marker residue in fish meat,
- extension of MRLs from terrestrial species to fish muscle and skin is directly possible when the parent compound is the marker residue and a MRL has been established in muscle of the reference species,
- a validated analytical method for the monitoring of residues of fluralaner in Salmonidae muscle and skin in natural proportions is available, indicating that residues in edible tissues can be adequately monitored,
- due to its design, the analytical method developed for Salmonidae is expected to be basically applicable for other fin fish,

the Committee recommends the extension of maximum residue limits for fluralaner from muscle of poultry to muscle and skin of Salmonidae. Furthermore, with reference to Article 5 of Regulation (EC) No 470/2009, the Committee recommends the extrapolation of the maximum residue limit for Salmonidae to fin fish. Therefore, the Committee recommends the amendment of the entry for fluralaner in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 in accordance with the following table:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Fluralaner	Fluralaner	Poultry	65 µg/kg 650 µg/kg 650 µg/kg 420 µg/kg 1300 µg/kg	Muscle Skin and fat in natural proportions Liver Kidney Eggs	NO ENTRY	Antiparasitic agents/ Agents against ectoparasites
		Fin fish	65 µg/kg	Muscle and skin in natural proportions		

Table 1 is updated with an entry only for fin fish, as this term includes Salmonidae.

Based on the recommended maximum residue limits the theoretical intake of residues from fish tissues and other food commodities represents approximately 60% of the ADI.

6. Background information on the procedure

Submission of the dossier: 24 April 2024

Steps taken for assessment of the substance:

- Application validated: 15 May 2024
- Clock started: 16 May 2024
- List of questions adopted: 12 September 2024
- Clock restarted: 18 November 2024
- CVMP opinion adopted: 12 February 2025