25 April 2018
EMA/CVMP/456716/2017
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Fluazuron (All ruminants, except bovine and ovine, and fin fish)

On 28 March 2018 the European Commission adopted a Regulation[1] establishing maximum residue limits for fluazuron in fin fish, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Fluazuron is intended for use in fin fish for the control of sea lice following application by the cutaneous route.

Maximum residue limits had previously been established for bovine[2] species. Farmacologia en Aquacultura Veterinaria FAV S.A. submitted to the European Medicines Agency an application for the extension of maximum residue limits on 20 April 2017.

Based on the data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 5 October 2017 the extension of maximum residue limits for fluazuron to fin fish and the extrapolation of the MRLs established in tissues of bovine species to tissues of other ruminants except sheep as well as to bovine milk.

Subsequently the Commission recommended on 6 February 2018 that maximum residue limits in all ruminants except bovine and ovine and fin fish are established. This recommendation was confirmed on 27 February 2018 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 28 March 2018.

[1] Commission Implementing Regulation (EU) No 2018/523, O.J. L 88, of 03 April 2018
[2] Commission Regulation (EC) No 1518/2005, O.J. L 244, of 20.09.2005

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Summary of the scientific discussion for the establishment of MRLs

Substance name:	Fluazuron
Therapeutic class:	Antiparasitic agents / Agents (acting) against ectoparasites
Procedure number:	EMEA/V/MRL/003471/EXTN/0002
Applicant:	Farmacologia en Aquacultura Veterinaria FAV S.A.
Target species applied for:	Fin fish
Intended therapeutic indication:	Control of sea lice
Route(s) of administration:	Cutaneous

1. Introduction

Fluazuron (CAS no. 86811-58-7) is an insect growth regulator belonging to the class of benzoylphenyl urea derivatives, a class of chitin synthesis inhibitors.

Fluazuron is used for tick control in beef cattle following cutaneous application as a pour-on at single dose levels of 1.5 and 2.5 mg/kg bw with a possible additional treatment after 3 to 6 months.

The intended use in fin fish is for the control of sea lice following application by the cutaneous route.

Fluazuron is not used in human medicine.

Fluazuron was previously assessed by the CVMP and a toxicological ADI of 0.043 mg/kg bw/day (or 2580 µg per day for a 60 kg person) was established.

Currently, fluazuron is included in 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
Fluazuron	Fluazuron	Bovine	200 µg/kg 7000 µg/kg 500 µg/kg 500 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption	Antiparasitic agents / Agents against ectoparasites

2. Scientific risk assessment

2.1. Safety assessment

The CVMP has previously assessed the consumer safety of fluazuron and established an ADI of 0.043 mg/kg bw (i.e. 2580 µg per day for a 60 kg person) based on the NOEL of 4.3 mg/kg bw/day for pathological changes in the uterus in a 2-year study in mice and a 100-fold safety factor. Therefore, no further assessment regarding the consumer safety of the substance is required for the purpose of this extension application.

2.2. Residues assessment

2.2.1. Pharmacokinetics in target species

No pharmacokinetic data in fish were provided for this extension application. Pharmacokinetic data in bovine species were previously assessed by the CVMP and are reported in the 2006 Summary Report recommending establishment of MRLs in cattle (EMEA/CVMP/126892/2006). These are copied below.

Following subcutaneous administration of radiolabelled fluazuron to steers a depot was formed at the injection site. Fluazuron was slowly released into the circulation, with a maximum level in plasma reached after 48 hours, and an elimination half-life in plasma of 78 days. After release, fluazuron was mainly taken up by the adipose tissues and to a lesser extent by other tissues. Depletion of fluazuron residues from the tissues, which consisted mainly of unchanged fluazuron, was slow. Ultimately, fluazuron was partially (for about one third) metabolised into more polar metabolites. Sixteen weeks after administration 16% of the administered dose was eliminated as unchanged fluazuron and 8% as its degradation products. The major route of elimination was the faeces (23% of the dose after 16 weeks), including bile, while renal excretion (1% of the dose after 16 weeks) was of minor importance. Although the fate of fluazuron in cattle was very similar to that in rats, the extent of metabolism appeared to be higher in rats compared to cattle.

When radiolabelled fluazuron was administered topically to cattle, it was slowly absorbed, either percutaneously, orally (by licking), or both. A steady state between absorption and elimination was observed for three to four weeks after treatment. The absorbed radiolabel was taken up mainly by adipose tissues and to a lesser extent by other tissues. Depletion of fluazuron from plasma and edible tissues was slow, with half-lives of elimination of 10.5 and 4.5 to 5.5 weeks, respectively. The major route of elimination was the faeces (62% of the dose after 16 weeks), while renal excretion was of minor importance (1% of the dose after 16 weeks). There was some indication of biliary excretion. Fluazuron was not extensively metabolized, as unchanged fluazuron generally accounted for more than 90% of the total residues in tissues and faeces. At the first time point (2 weeks), fluazuron accounted for 90% of the total residues in liver, 99% in kidney, 97% in muscle, and 100% in fat. Comparing topical administration to subcutaneous administration, the pattern of metabolites excreted in faeces was somewhat more complex after subcutaneous administration (with about one-third of the fluazuron metabolised into more polar metabolites). Although the fate of fluazuron in rats was similar to that in cattle, they metabolised fluazuron to a greater extent than cattle.

2.2.2. Residue depletion studies

No residue data in fish were provided for this extension application. Residue data in bovine species were previously assessed by the CVMP and are reported in the 2006 Summary Report recommending establishment of MRLs in cattle (EMEA/CVMP/126892/2006). These are copied below.

Several residue studies with fluazuron were performed in cattle. In addition, some residue data were available from field trials. In all studies, the method of administration was in accordance with the recommended therapeutic use (1.5 to 2.5 mg/kg bw). In some studies higher doses were used, up to 4 mg/kg bw. In several studies, treatment was repeated after 12 weeks, the minimal recommended interval, or already after 9 weeks. Also the transfer of residues from treated dams to their calves via the milk was studied.

Four weeks after a single topical dose of 2 mg/kg bw, fluazuron concentrations were highest in fat (2.4 mg/kg). Lower residue concentrations were found in liver (0.10 mg/kg), kidney (0.07 mg/kg) and muscle (0.07 mg/kg). The residue concentrations in fat declined slowly to 0.5 mg/kg at 16 weeks after treatment. This residue pattern and depletion were confirmed by the other single dose studies. In general,

the residue concentrations in fat were approximately ten times higher than in other tissues. There was no difference in the residue concentrations in subcutaneous fat from the application site and in fat from other locations (subcutaneous, renal or omental).

Six weeks after topical doses of 3 mg/kg bw given twice at an interval of 9 weeks, fluazuron concentrations were highest in fat (1.18 mg/kg). Lower residue concentrations were found in liver (0.09 mg/kg), kidney (0.04 mg/kg) and muscle (less than 0.04 mg/kg). The residue concentrations in fat declined slowly to 1.31 mg/kg at 16 weeks after treatment. This residue pattern and depletion were confirmed by the other repeated dose studies. In general, the residue concentrations in fat were several times higher than in other tissues. There was no difference in the residue concentrations in subcutaneous fat from the application site and in fat from other locations (subcutaneous or renal).

Six weeks after topical doses of 4 mg/kg bw given three times at intervals of 12 weeks, fluazuron concentrations in fat samples taken by biopsy were 2.1 to 3.0 mg/kg. The residue concentrations in plasma and in fat were less following the second treatment and less again following the third treatment.

Fluazuron was excreted via cows' milk to calves, finally resulting in higher plasma and fat residue levels in calves than in the cows. Multiple treatments with 12-week intervals did not lead to accumulation of residues, although the residues following treatment in spring tended to be higher, maybe due to grooming of the winter coats.

Selection of marker residue and ratio of marker to total residues

Fluazuron is poorly metabolised and was therefore selected as the marker residue for cattle tissues, where the ratios of marker to total residues were established as 0.97 in muscle, 1.0 in fat, 0.90 in liver and 0.99 in kidney.

As indicated in the CVMP note for guidance on the establishment of maximum residue limits for *Salmonidae* and other fin fish (EMEA/CVMP/153b/97-FINAL) metabolism in fin fish is generally less complex than in mammalian species. In line with the note for guidance, as fluazuron is poorly metabolised in a major mammalian species, the parent compound is considered an appropriate marker residue for use in monitoring residues of fluazuron in fin fish.

2.2.3. Monitoring or exposure data

No monitoring or exposure data other than that described elsewhere in this report were available.

2.2.4. Analytical method for monitoring of residues

A sufficiently validated HPLC-UV method was proposed for the routine monitoring of fluazuron in edible tissues of bovine species. The method was described according to an internationally recognised format closely resembling ISO 78/2. Although the method as such was deficient with respect to specificity, a highly specific LC-MS method was present in the dossier for confirmatory purposes. The limit of quantification was established at 100 µg/kg for muscle, 200 µg/kg for liver and kidney and 1000 µg/kg for fat.

A new UPLC-MS/MS method for the determination of residues of fluazuron in muscle and skin in Salmonidae and other fin fish has been developed. The method is based on fluazuron as the marker residue, as for the currently approved MRL for bovine muscle. The method was sufficiently described according to an internationally recognised format closely resembling ISO 78/2, and adequately validated in muscle and skin from salmon. The limit of quantification was established at 50 µg/kg.

The relevant European Reference Laboratory (EURL) has reviewed the analytical method and is in agreement with the above conclusions but pointed out that the CHMP Guideline on bioanalytical method

validation (EMEA/CHMP/EWP/192217/2009) would require additional data on matrix effects. However, as this guideline does not apply to MRL applications no further action was taken.

It was concluded that a suitable analytical method for monitoring the levels of the residues of fluazuron in muscle and skin in fin fish is available.

2.2.5. Findings of EU or international scientific bodies

Fluazuron was evaluated by the 48th Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) leading to Codex MRLs in cattle of 7000 µg/kg in fat, 200 µg/kg in muscle, and 500 µg/kg in liver and kidney; these are the same as those established in the EU.

3. Risk management considerations

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

As fluazuron is not known to have antimicrobial properties investigation of potential effects on microorganisms used for industrial food processing was not considered necessary.

3.2. Other relevant risk management considerations for the establishment of maximum residue limits

No relevant factors were identified for consideration of the risk management recommendations.

3.3. Elaboration of MRLs

For the evaluation of this application for the extension of MRLs for fluazuron to fin fish the CVMP Note for guidance on the establishment of maximum residue limits for *Salmonidae* and other fin fish (EMEA/CVMP/153b/97-FINAL) was taken into account. As indicated in the note for guidance metabolism in fin fish is generally less complicated than in mammalian species. The note for guidance indicates that where an MRL has been established for a substance in muscle in a major mammalian species it may be applied to *Salmonidae* and other fin fish.

In line with the above note for guidance, and considering that available data indicate that fluazuron is poorly metabolised and that the established marker residue is the parent compound, the MRL established for bovine muscle (200 µg/kg) can be safely applied to fin fish (where the relevant tissue is muscle and skin in natural proportions).

The theoretical maximum daily intake calculated on the basis of the MRLs established for cattle tissues represents 19% of the ADI. The establishment of an MRL of 200 µg/kg for fin fish is not expected to impact on this.

3.4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation No 470/2009 the CVMP considered the possibility of extrapolating the maximum residue limits established in bovine species to other food producing species and commodities. Taking into account the provisions laid down in Regulation No 2017/880, the recommendations on extrapolation are justified as follows:

<table>
<tr><th>Animal species/ food commodities</th><th>Extrapolation possible (Yes/No)</th><th>Justification</th></tr>
<tr><td>All ruminants except sheep</td><td>Yes</td><td>In line with Regulation 2017/880, extrapolation of cattle MRLs to minor ruminants can be accepted.</td></tr>
<tr><td>Sheep</td><td>No</td><td>No data on pharmacokinetics or residues in sheep are available. The possible extrapolation from a major species to a related major species (i.e. from cattle to sheep (tissues)) is not covered by Regulation 2017/880. Furthermore, the CVMP considers that MRLs cannot be extrapolated to sheep without supporting data demonstrating similarity of metabolism.</td></tr>
<tr><td>Milk</td><td>Yes</td><td>In view of the limited metabolism of fluazuron and the large portion of the ADI still available (approximately 80%), extrapolation to bovine milk would be possible, in accordance with Regulation No 2017/880.

Further extrapolation to milk of food producing species other than bovine is not possible as this would involve a double extrapolation.

The lowest established MRL can be used as a point of departure for the MRL for milk. The lowest MRL is 200 µg/kg (bovine muscle). Using this value for milk, and in addition applying the lowest ratio of marker to total residues (0.9 in bovine liver) to milk, the TMDI would be 826 µg:
<table>
<tr><th></th><th>MRL (µg/kg)</th><th>consumption (kg)</th><th>ratio M/T</th><th>intake (µg)</th></tr>
<tr><td>Muscle</td><td>200</td><td>0,3</td><td>0,97</td><td>61,86</td></tr>
<tr><td>Fat</td><td>7000</td><td>0,05</td><td>1</td><td>350,00</td></tr>
<tr><td>Liver</td><td>500</td><td>0,1</td><td>0,9</td><td>55,56</td></tr>
<tr><td>Kidney</td><td>500</td><td>0,05</td><td>0,99</td><td>25,25</td></tr>
<tr><td>milk</td><td>200</td><td>1,5</td><td>0,9</td><td>333,33</td></tr>
<tr><td></td><td></td><td></td><td></td><td>826,00</td></tr>
</table>
This maximum intake equates to 32% of the ADI. Therefore, no further adjustment of the value of 200 µg/kg is necessary to take account of the physicochemical properties of the substance, and the MRL for milk can be set at 200 µg/kg.</td></tr>
<tr><td>Pigs</td><td>No</td><td>No data on pharmacokinetics or residues in pigs are available. As pigs are unrelated to cattle, the species for which data are available, and in line with Regulation 2017/880, MRLs cannot be extrapolated to pigs without supporting data demonstrating similarity of metabolism.</td></tr>
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Horses	No	No data on pharmacokinetics or residues in horses are available. As horses are unrelated to cattle, the species for which data are available, as available data in rats suggests that there may be differences in the metabolism of fluazuron in monogastric species (including horses) compared to in cattle, and as specific data on metabolism in horses are not available, in line with Regulation 2017/880, MRLs cannot be extrapolated to horses.
Rabbits	No	No data on pharmacokinetics or residues in rabbits are available. As rabbits are unrelated to cattle, the species for which data are available, as available data in rats suggests that there may be differences in the metabolism of fluazuron in monogastric species (including rabbits) compared to in cattle, and as specific data on metabolism in rabbits are not available, in line with Regulation 2017/880, MRLs cannot be extrapolated to rabbits.
Poultry (including eggs)	No	No data on pharmacokinetics or residues in poultry are available. As poultry are unrelated to cattle, the species for which data are available, and in line with Regulation 2017/880, MRLs cannot be extrapolated to poultry without supporting data demonstrating similarity of metabolism.
Honey	No	No data on residues in honey are available. In the absence of such data, and in line with Regulation 2017/880, MRLs cannot be extrapolated to honey.

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

Having considered that:

- the toxicological ADI of 0.043 mg/kg bw (i.e. 2580 µg/person) was established as the overall ADI for fluazuron;
- the marker residue established for cattle tissues, fluazuron, can also be retained as the marker residue for fin fish;
- the ratios of marker to total residues established in cattle were 0.97 in muscle, 1.0 in fat, 0.90 in liver and 0.99 in kidney; the ratio of marker to total residues established for cattle muscle can be considered to apply for muscle and skin of fin fish,
- extrapolation of a maximum residue limits to all ruminants except sheep and to bovine milk is considered appropriate,
- a validated analytical method for the monitoring of residues of fluazuron in edible fin fish is available;
- although it was not specifically demonstrated, the analytical methods available for monitoring of residues in tissues of cattle are expected to be basically applicable for monitoring of residues in tissues of other ruminants, as well as in milk from cattle;

the CVMP recommends the extension of the maximum residue limits established for fluazuron in bovine muscle to muscle (muscle and skin in natural proportions) of fin fish. Furthermore, and with reference to Article 5 of Regulation (EC) No 470/2009, the MRLs established in tissues of bovine species can be extrapolated to tissues of other ruminants except sheep as well as to bovine milk, in accordance with the following table:

Pharmaco-logically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Fluazuron	Fluazuron	All ruminants except bovine and ovine	200 µg/kg 7000 µg/kg 500 µg/kg 500 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption	Antiparasitic agents / Agents (acting) against ectoparasites
		Bovine	200 µg/kg 7000 µg/kg 500 µg/kg 500 µg/kg 200 µg/kg	Muscle Fat Liver Kidney Milk	No entry	
		Fin fish	200 µg/kg	Muscle and skin in natural proportions	No entry	

Based on these MRLs, the theoretical maximum daily intake corresponds to 32% of the ADI.

4. Background information on the procedure

Submission of the dossier

Steps taken for assessment of the substance

Application validated:	10 May 2017
Clock started:	11 May 2017
Opinion adopted:	5 October 2017