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SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Veterinary Medicinal Products

European public MRL assessment report (EPMAR)

Praziquantel (fin fish)

On 17 May 2023, the European Commission adopted a Regulation[1] establishing maximum residue limits for praziquantel in fin fish. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Veterinary Medicinal Products.

Praziquantel is intended for use in fin fish for the treatment of ectoparasitic infestations of the gills at a dose of 150 mg/kg bodyweight/day for 3 consecutive days via feed.

Maximum residue limits had already been established for praziquantel in ovine species and *Equidae* (No MRL required classification).

Vethellas AEBE submitted to the European Medicines Agency an application for the extension of maximum residue limits on 27 July 2021.

Based on the original and complementary data in the dossier, the Committee for Veterinary Medicinal Products recommended, on 8 September 2022, the extension of maximum residue limits for praziquantel to fin fish. Furthermore, and with reference to Article 5 of Regulation (EC) No 470/2009, the Committee recommended that the "no MRL required" entry established in ovine species be extrapolated to other ruminants except cattle.

Subsequently, the Commission recommended, on 23 March 2023, that numerical maximum residue limits in fin fish as well as a "No MRL required" classification for all ruminants except bovine and Equidae are established. This recommendation was confirmed on 1 April 2023 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 17 May 2023.

[1] Commission Implementing Regulation (EU) No 2023/981, O.J. L 134, of 22.05.2023

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Summary of the scientific discussion for the establishment of MRLs

Substance name:	Praziquantel
Therapeutic class:	Antiparasitic agents/Agents acting against endo- and ectoparasites
Procedure number:	EMEA/V/MRL/003477/EXTN/0004
Applicant:	VETHELLAS AEBE
Target species requested:	Fin fish
Intended therapeutic indication:	Treatment of ectoparasitic infestations of the gills
Route(s) of administration:	Oral

Introduction

Praziquantel is an antiparasitic substance commonly used in human and veterinary medicinal products to treat helminth infections.

Praziquantel is intended for use in fin fish for the treatment of ectoparasitic infestations of the gills caused by monogenean trematodes principally of the species *Sparicotyle chrysophrii*. It is intended to be administered at a dose of 150 mg/kg bodyweight (bw)/day for 3 consecutive days via feed.

Praziquantel was previously assessed by the CVMP, and a toxicological ADI of 0.17 mg/kg bw, i.e. approximately 10 mg/person when considering a bodyweight of 60 kg, was established.

Currently, praziquantel is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 of 22 December 2009 in accordance with the following table:

Pharmaco-logically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Praziquantel	NOT APPLICABLE	Ovine, *Equidae*	No MRL required	NOT APPLICABLE	NO ENTRY	NO ENTRY

1. Scientific risk assessment

1.1. Safety assessment

The CVMP has previously assessed the consumer safety of praziquantel and established an ADI of 0.17 mg/kg bw, i.e. approximately 10 mg/person based on a NOEL of 33 mg/kg bw from a 4-week study conducted in rats and applying a safety factor of 200. Therefore, no further assessment regarding the consumer safety of the substance is required for the purpose of this extension application, and no changes to the established ADI of 0.17 mg/kg bw are proposed.

1.2. Residues assessment

The applicant provided justification for submitting a reduced data package based on the provisions of Commission Regulation (EU) No 2018/782 (Annex II, paragraph II.1. – Availability of alternative medicines). However, considering that the application relates to fin fish, which includes salmon (a

major species in the context of an MRL assessment as outlined in Article 2 of Commission Regulation (EU) 2017/880), reference to the MUMS/limited market guidance is inappropriate. That said, it is acknowledged that the CVMP "Note for guidance on the establishment of maximum residue limits for *Salmonidae* and other fin fish" (EMEA/CVMP/153b/97-Final), which recognises that a pragmatic approach, as adopted in guidelines for minor species, should also apply to the establishment of MRLs for substances used in Salmonidae and other fin fish. The pragmatic approach outlined in that note for guidance takes the following points into account:

- "[T]o date, for substances that have been evaluated, the marker residue determined for any given substance used in Salmonidae has been identical to that established in other animal species;
- the target tissue considered appropriate for salmonidae is muscle, including skin in natural proportions, and that in salmonidae muscle is not a tissue where significant metabolism occurs;
- even though available data comparing the metabolism of veterinary drugs in salmonidae and other animal species are rather scarce, significant differences between the metabolic profile of substances used in fish and other species are not apparent;
- the only difference in metabolism of medicines in fish and other species appears to be 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".

In view of this established CVMP principle, and noting that praziquantel has been reviewed in the context of an MRL assessment for both sheep (a major ruminant species) and horses (a minor monogastric species), a pragmatic approach has been adopted when reviewing and concluding on the reduced data package that has been provided in support of the present MRL extension application to fin fish.

1.2.1. Pharmacokinetics in target species

No original pharmacokinetic data in fin fish were provided. Instead, reference was made to published literature and the CVMP summary reports for praziquantel.

Pharmacokinetic data in ovine species were previously assessed by the CVMP as outlined in the summary report establishing MRLs for non-lactating sheep in 1996 (EMEA/MRL/141/96-FINAL) as well as in the subsequent summary report describing the extension of MRLs to sheep milk (EMEA/MRL/523/98-FINAL). The CVMP also previously assessed pharmacokinetic data in horses as reported in the summary report establishing the extension of MRLs to horses in 1998 (EMEA/MRL/337/98-FINAL). It was concluded that there was no need to establish an MRL for praziquantel in ovine species or *Equidae*. The relevant information extracted from the above-mentioned summary reports is detailed below:

"The metabolism of praziquantel was investigated in two sheep given a single oral dose of radiolabelled ^{14}C-praziquantel at 10 mg/kg bw and sacrificed 8 hours post treatment. Thirty-five to 50% of the dose was excreted in urine in the 8-hour period: faeces accounted for only approximately 1% of the dose. At sacrifice, the highest radioactivity concentrations were measured in kidney (5.46–8.15 µg/g), liver (5.35–7.58 µg/g), with low concentrations in muscle (0.45–0.52 µg/g) and fat (0.16–0.21 µg/g). Unchanged parent compound was a minor component (less than 10%) of the extractable radioactivity in the edible tissues present only in liver and fat. Besides the parent compound seven metabolites were identified. The percentage ratio of these metabolites one to the other varied between 3% and 13% in the different tissues".

"A residue study using ^{14}C-praziquantel was conducted in sheep given an oral dose of 3.75 mg/kg bw. The study confirmed the rapid absorption of praziquantel, peak plasma concentration being reached within 2 hours of dosing. A half-life of 4.2 hours was determined and excretion from plasma was rapid. Eighty-eight percent of the total dose administered was excreted within 24 hours; 98% within 72 hours [...]".

"Radiolabelled metabolism studies with ^{14}C-Praziquantel in lactating sheep also demonstrate extensive metabolism; parent compound was not detected in milk of sheep given 3.75 mg/kg bw; 11 metabolites were found of which 8 were identified and characterised. All metabolites found in milk were also found to exist in edible tissues of treated sheep".

In summary, it was concluded that praziquantel is rapidly and extensively detoxified and excreted in sheep.

"The plasma concentration profile in horses treated orally with ^{14}C-praziquantel showed that maximum plasma concentrations were reached approximately 30 minutes after treatment with 1 mg/kg bw. The peak plasma concentration was 0.127 mg equivalents/ml while the 24-hour mean plasma level was 0.014 µg equivalents/ml. Urinary excretion accounted for 31% of the administered dose within 24 hours while faecal excretion accounted for a further 24% of the dose".

Pharmacokinetic data on praziquantel in a range of fish species from the published literature have been provided for this MRL extension application. No pharmacokinetic data on praziquantel in the intended target species, gilthead sea bream, were provided. After oral administration of between 10–150 mg/kg bw praziquantel, maximum plasma concentrations ranging from 0.36–14.22 µg/ml were reported. Depending on the fish species, maximum plasma concentrations were measured within 0.5–8 hours, with elimination half-lives of 6.57–15.1 hours. In comparison, following an oral dose of 3.75 mg/kg bw to sheep, peak plasma concentration was reached within 2 hours of dosing, with a half-life of 4.2 hours. Elimination in fish would appear to be slower than that observed in mammals, likely due to differences in metabolic capacity.

Praziquantel has been reported previously by the CVMP to be rapidly and extensively metabolised in rats, dogs, monkeys and sheep, with all major metabolites being hydroxylated derivatives of the parent compound. Metabolism was investigated in one species of fish (kingfish, *Seriola lalandi*), identifying at least 7 mono- or di-hydroxylated derivatives of praziquantel, similar to findings in mammals.

The applicant notes that praziquantel is distributed throughout fish tissues following oral administration. In particular, the highest concentrations were found in the liver and kidney, while the lowest concentrations were found in skin, muscle and skin mucous. In the case of sheep, the highest concentrations of praziquantel were also found in the liver and kidney following oral administration.

Following single oral administration of doses ranging from 10–150 mg/kg bw, praziquantel peak concentrations in liver ranged from 2.70–42.52 µg/g after 0.5–10 hours, while, in kidney, peak concentrations ranged from 2.99–12.88 µg/g after 0.5–1.0 hours. In comparison, observed peak concentrations in muscle were reported to range from 0.51–5.41 µg/g after 0.5–1.0 hours. There are many factors that could explain the differences in the peak praziquantel concentrations observed in the published studies: namely, different doses, single or repeat treatments, administration via feed or by gastric intubation, different environmental conditions, as well as possible differences in metabolism in different fish species.

Differences in the rate of metabolism between mammals and fish (i.e. poikilotherms) can be expected due to differences in body temperature. As stated in the CVMP "Note for guidance on the establishment of maximum residue limits for *Salmonidae* and other fin fish" (EMEA/CVMP/153b/97-

FINAL), "the only difference in metabolism of medicines in fish and other species appears to be 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". The study reported by Tubbs et al. (2008)[2] would tend to support that general principle in that the metabolism of praziquantel in kingfish was reported to parallel findings in mammals.

In conclusion, it is acknowledged that the available pharmacokinetic data are heterogenous in nature such that it is not possible to reach definitive conclusions on the pharmacokinetic profile in fin fish generally. In addition, the data are inadequate to robustly characterise metabolism/metabolites with the result that, for residues, the ratio of parent compound to total residue cannot be determined. Notwithstanding the deficiencies highlighted, the pharmacokinetic data provided can be considered adequate for the purposes of this specific application.

1.2.2. Residue depletion studies

No original residue depletion studies in fin fish were provided. Instead, the findings of residue studies in different fish species from the published literature have been presented. Two of the published studies were conducted in the intended target species, gilthead sea bream.

Residue studies in ovine species were previously assessed by the CVMP as outlined in the summary report establishing MRLs for non-lactating sheep in 1996 (EMEA/MRL/141/96-FINAL) and the subsequent extension of MRLs to sheep milk (EMEA/MRL/523/98-FINAL). Residue studies in horses were also assessed previously by the CVMP, as detailed in the summary report establishing MRLs for horses in 1998 (EMEA/MRL/337/98-FINAL). The relevant information extracted from the above-mentioned summary reports is detailed in the following section ("Depletion in tissues").

Depletion in tissues

"A residue study using ^{14}C-praziquantel was conducted in sheep given an oral dose of 3.75 mg/kg bw. [...] At 8 hours post treatment, the maximum levels present in tissues of 4 sheep were as follows: liver, 2.87 µg equivalent/g; kidneys, 2.55 µg equivalent/g; muscle 0.19 µg equivalent/g; and fat, 0.13 µg equivalent/g. Ingestion of total residues from edible tissues at this time amounts to 0.48 mg. This is some 20 times lower than the ADI. After 24 hours post treatment, levels in muscle and fat were 0.02 µg equivalent/g. At this time mean levels of 0.56 µg equivalent/g and 0.3 µg equivalent/g were present in the liver and kidney".

"Radiolabelled residue depletion studies with ^{14}C-Praziquantel in lactating sheep given 3.75 mg/kg bw show that residues in sheep milk are rapidly depleted. At 8 hours post treatment, the maximum level present in milk was 1.6 µg equivalents/ml; at 48 hours the maximum level was 0.2 µg equivalents/ml and by 72 hours it had declined to a maximum of 0.04 µg equivalents/ml".

"Two groups of 4 horses were administered ^{14}C-praziquantel in a commercial formulation at 1 mg/kg bw as a single dose and slaughtered after 8 or 24 hours. At 8 hours post treatment, the maximum levels present in tissues were as follows: 2.44 µg equivalents/g in liver, 1.62 µg equivalents/g in kidneys, 0.14 µg equivalents/g in muscle and 0.12 µg equivalents/g in fat. At 24 hours post treatment, the maximum levels present in tissues were as follows: 0.36 µg equivalents/g in liver, 0.18 µg equivalents/g in kidneys, 0.02 µg equivalents/g in muscle and less than 0.01 µg equivalents/g in fat".

In the absence of original (proprietary) residue depletion studies in fin fish, published literature

[2] L Tubbs, T Mathieson, M Tingle (2008): Metabolism of praziquantel in kingfish *Seriola lalandi*. Dis Aquat Organ. 78(3):225–33.

investigating the depletion of praziquantel residues in the tissues of different fish species was provided. The dose and duration of treatment varied, ranging from 10–500 mg/kg bw, and from single doses up to six consecutive days of treatment. From the literature provided, the highest reported mean concentration of praziquantel in fish muscle, 24 hours post treatment, was 3.610 ± 0.24 µg/g following a single 400 mg/kg bw dose to rockfish by gastric intubation. In comparison, it was reported that treatment of rockfish with three consecutive daily doses of 400 mg/kg bw praziquantel in feed resulted in a mean concentration of praziquantel in muscle of 1.20 ± 0.80 µg/g. The available data indicate that praziquantel does not accumulate in muscle tissue of fin fish.

The applicant notes that the recommended dose of 150 mg/kg bw is unlikely to be exceeded when administered orally, due to the bitterness of the drug causing palatability problems in various species of fish. As such, a study reported that intake of feed containing praziquantel was reduced in treated gilthead sea bream when medicated feed was administered to achieve doses of praziquantel of 200 and 400 mg/kg bw as follows: Based on recorded feed intake, the actual doses achieved were 158.1 mg/kg bw and 116.3 mg/kg bw, respectively.

Two residue studies from the published literature were conducted in gilthead sea bream. The first study investigated the concentration of praziquantel residues in muscle plus skin following the proposed treatment of 150 mg/kg bw/day for 3 days when administered as feed with oil-coated praziquantel[3]. Mean praziquantel concentrations of 0.04 µg/g were reported 24 hours post treatment, with residues below the limit of quantification (LOQ) of 0.04 µg/g by 48 hours. In the second study[4], gilthead sea bream were treated via feed with praziquantel at a dose of 50 mg/kg bw for 6 consecutive days. The mean concentration of praziquantel in fish muscle after six days of treatment was 0.05 µg/g. While the GLP status of these studies is unknown, in the opinion of the CVMP, they provide useful information on residue concentrations that would typically occur based on the proposed use of praziquantel in gilthead sea bream. Consequently, the applicant has taken the intended use into account and focused on the published studies in gilthead sea bream, i.e. reported mean praziquantel residue concentrations of 0.04 µg/g, 24 hours after the last treatment (via feed at a dose of 150 mg/kg bw for 3 days), with residues below the LOQ of 0.04 µg/g in all samples by 48 hours. However, as praziquantel will be used in fin fish, the reported worst-case mean concentration of praziquantel in fish muscle of 3.610 µg/g at 24 hours was considered by the CVMP. Although this residue finding did not result from the dosing regimen proposed, when calculating possible consumer exposure to residues, potential dosing regimens for fin fish generally also need to be considered.

Selection of marker residue and ratio of marker to total residues

For fin fish, the parent compound praziquantel has been proposed as the marker residue.

It should be noted that, as no marker residue was established by the CVMP for sheep or horses, no information on the ratio of marker to total residues (MR/TR ratio) in other species is available.

Praziquantel has been reported previously by the CVMP to be rapidly and extensively metabolised in rats, dogs, monkeys and sheep, with all major metabolites being hydroxylated derivatives of the parent compound. No marker residue was identified by the CVMP for sheep or horses. The very limited metabolic data in fish (kingfish [*Seriola lalandi*]) identified at least 7 mono- or di-

[3] D Kogiannou, G Rigos (2021): Praziquantel depletion from muscle plus skin tissue of gilthead sea bream (*Sparus aurata*). Medit Mar Sci. 22(1):121–24.
[4] E Baralla, MV Varoni, M Nieddu, MP Demontis, P Merella, C Burreddu, G Garippa, G Boatto (2020): Determination of praziquantel in *Sparus aurata* L. after administration of medicated animal feed. Animals (Basel). 10(3):528.

hydroxylated derivatives of praziquantel, similar to findings in mammals.

In the CVMP "Note for guidance on the establishment of maximum residue limits for *Salmonidae* and other fin fish" (EMEA/CVMP/153b/97-FINAL), it is stated that "the parent compound is normally acceptable as a valid marker residue in *Salmonidae* and other fin fish". Therefore, where a numerical MRL is required, the parent compound could normally be accepted.

While selection of praziquantel as a marker residue in fin fish may be questioned on the basis that praziquantel is rapidly and extensively metabolised in mammals, the CVMP is prepared to accept it as the marker residue noting that:

- this is provided for in the CVMP "Note for guidance on the establishment of maximum residue limits for *Salmonidae* and other fin fish" (EMEA/CVMP/153b/97-FINAL);
- the available information from the published literature on praziquantel depletion in fish tissues indicates that parent praziquantel is detectable in fish muscle for several days after treatment; and
- the proposed marker residue and MRL are the same as that established in another territory for fish and can be considered to facilitate trade.

Noting that praziquantel is a racemate, and as it is unknown which of the two enantiomers is toxicologically relevant, the marker residue should be the sum of the isomers.

Given the limited availability of information on metabolism in fin fish, a conservative MR/TR ratio of 0.1 is applied in order to take into account unquantified praziquantel metabolites.

1.2.3. Monitoring or exposure data

No monitoring or exposure data were available.

1.2.4. Analytical method for monitoring of residues

An LC-MS/MS method has been presented for the determination of residues of praziquantel and its metabolite *cis*-hydroxy praziquantel in edible tissues of gilthead sea bream (muscle and skin in natural proportions) and has been shown to be applicable to edible tissue of Atlantic salmon (muscle and skin in natural proportions). The method was broadly conducted in accordance with VICH GL49, although a number of deficiencies in the documentation presented were noted. The limit of quantification for praziquantel is considered to be 5 µg/kg. Based on the information provided, the CVMP accepts that the marker residue, praziquantel, can be adequately measured in edible tissues originating from fin fish.

The relevant EURL has reviewed the method and is in agreement with the above assessment of the validation of the analytical method: while the method is capable of controlling the proposed MRL of 20 µg/kg and it allows praziquantel to be detected at the LOQ of 5 µg/kg, it has not been fully validated in accordance with standard requirements.

Notwithstanding the deficiencies in the documentation provided, the CVMP is of the opinion that additional information on method validation is not necessary in order to conclude on the current application, noting that, in this particular case, the full validation of the analytical method is not required to support or confirm pivotal residue depletion data because these were not the basis for the establishment of the MRL for praziquantel in fin fish. Further, the CVMP noted that, in any future application for marketing authorisation for praziquantel in fin fish, a fully validated analytical method

in support of residue depletion studies will be required.

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

As the substance does not possess antimicrobial activity, no effects on microorganisms used for industrial food processing are expected.

1.2.6. Findings of EU or international scientific bodies

Praziquantel has not been evaluated for this purpose by other EU scientific bodies.

A temporary limit for fish muscle of 20 µg/kg praziquantel has been set by the Australian Pesticides and Veterinary Medicines Authority (APVMA). The associated publicly available information indicates that this is a temporary MRL "set at or about the limit of analytical quantitation".

2. Risk management recommendations

2.1. Availability of alternative medicines and other legitimate factors

Availability of alternative medicines

Limited alternative veterinary medicinal products are available for use in fin fish for the treatment of ectoparasitic infestations of the gills caused by monogenean trematodes principally of the species *Sparicotyle chrysophrii*. A single product containing formaldehyde approved nationally for the treatment and control of external parasitosis by *Sparicotyle chrysophrii* in gilthead sea bream (*Sparus aurata*) is available as a dip solution.

Other factors that should, if applicable, be taken into consideration in support of the MRL recommendation:

- Prior to harvesting, it is standard practice for farmed fish to be subjected to a period of feed deprivation in order to avoid contamination of the resulting food product. This period varies according to temperature, species and feeding rate, but is reported to range from 1.5–5 days.
- The recommended dose of 150 mg/kg bw is unlikely to be exceeded when praziquantel is administered orally, due to the bitterness of the compound causing palatability issues in various species of fish.

Additional other relevant factors identified for consideration of the risk management recommendations:

- If a product were developed specifically for gilthead sea bream, off-label use for the treatment of parasitic infestations in other fish species would be possible, namely in Atlantic salmon.

2.2. Elaboration of MRLs

Based on the intended use, the applicant has proposed an MRL for fin fish. The applicant requests the extension of the established "No MRL required" status from ovine, a major food-producing species to

fin fish. As fin fish also include *Salmonidae*, the extension would be from a major species to a major species. Where a "No MRL required" status cannot be established, a numerical MRL has also been proposed.

Article 6 of Commission Regulation (EU) 2017/880 allows for extrapolation of a "No MRL required" status to an unrelated species, but only if the metabolism is similar. While, in general, metabolism in fin fish is expected to be comparable to but slower than that in mammals, the available pharmacokinetic data relating to praziquantel in fin fish are heterogenous. The data suggest that, in some fish species, treatment with praziquantel could result in residue levels in muscle that would have the potential to lead to consumer exposure exceeding the ADI (see below for details). Consequently, it is not considered appropriate to extend the "No MRL required" status for praziquantel to fin fish generally.

In the absence of an original (proprietary) residue depletion study, the applicant has used residue data from the published literature. The published study chosen to determine the residue burden in the standard food basket was conducted in gilthead sea bream at the intended dose of 150 mg/kg bw/day for 3 consecutive days via feed. Taking into account the observed depletion of praziquantel residues, the concentration in muscle plus skin of 0.04 µg/g one day after the last treatment was selected. The CVMP notes that this is a mean measured concentration. However, this is unlikely to significantly alter the used portion of the ADI established previously by the CVMP. As it is unknown if the water temperature used in the study represents the worst case for residues in gilthead sea bream, it may not accurately reflect the portion of the ADI that will be used. As noted previously, as the praziquantel MRL will apply to fin fish generally (that is, not limited to gilthead sea bream), the reported worst-case mean concentration of praziquantel reported in fish muscle/skin has not been considered by the applicant.

While acknowledging the limitations of the available dataset, based upon the residue depletion data from the published literature in gilthead sea bream, a praziquantel concentration in muscle plus skin at 24 hours of 0.04 mg/kg, following administration of a dose of 150 mg/kg bw/day for 3 consecutive days via feed, is considered to be supportive in predicting the theoretical daily intake of residues for the consumer exposed to foodstuffs derived from gilthead sea bream. The theoretical consumer intake of residues from fish tissues at 24 hours post treatment is calculated to be 0.012 mg, based on the edible portion for fish in the standard food basket of 300 g of muscle plus skin in natural proportions. This represents less than 0.118% of the overall ADI (10.2 mg/person/day). While this does not take into account unquantified praziquantel metabolites, the low portion of the ADI used is considered to provide a sufficient margin of safety for any uncertainties (even if a MR/TR ratio of 0.1 is incorporated into the consumer exposure calculation, intake would only represent a little over 1% of the ADI).

Recognising that the MRL entry will be for fin fish, the worst-case residue data at 24 hours from the published literature provided with the application has also been considered. A mean praziquantel concentration in muscle of rockfish of 3.61 mg/kg bw, 24 hours following administration of a single dose of 400 mg/kg bw by gastric intubation, was reported. It is noted that concentrations of praziquantel were reported for muscle only and not for muscle plus skin. The theoretical consumer intake of residues from fish tissues at 24 hours post treatment is calculated to be 1.083 mg, based on the edible portion for fish in the standard food basket (300 g of muscle plus skin in natural proportions). Considering the above figure, the maximum theoretical consumer intake represents 10.6% of the ADI. However, in order to take into account unquantified praziquantel metabolites, a precautionary MR/TR ratio of 0.1 would result in the ADI being exceeded at 106%.

When mean praziquantel concentrations in tissues 1–9 hours post administration are considered, mean residues in excess of 4 mg/kg have been reported in the muscle of Japanese amberjack

(*Seriola quinqueradiata*), skin of yellowtail kingfish (*Seriola lalandi*) and muscle of rockfish (*Sebastes schlegeli*). Taking into account a precautionary MR/TR ratio of 0.1, this would result in a theoretical consumer intake of > 12 mg, representing > 117% of the ADI.

In comparison, the theoretical daily consumer intake based on total residues from both edible tissues and milk of the major species sheep at 8 hours post treatment represents less than 30% of the ADI. In the case of horses, the theoretical daily consumer intake of residues at 8 hours post treatment represents less than 4% of the ADI. Of these, total residues in muscle represent approximately 0.6% and 0.42% of the ADI in sheep and horses, respectively.

In view of the above, the CVMP has concerns that the ADI for praziquantel could be exceeded in some fin fish species following treatment, thus posing a potential risk to the consumer. Given the uncertainties in terms of pharmacokinetics and residue depletion in fin fish, it is not possible to refine the consumer exposure estimates further. Given that it cannot be assured that consumer exposure to residues shall always remain at safe levels (i.e. below the ADI), it is not considered appropriate to accept a "No MRL required" classification in this case. Accordingly, a numerical MRL has been proposed.

When considering a numerical MRL, the temporary limit set by the Australian Pesticides and Veterinary Medicines Authority (APVMA) for fish muscle of 20 µg/kg praziquantel is referenced by the applicant. The associated publicly available information indicates that this is a temporary MRL "set at or about the limit of analytical quantitation". Taking this into account and considering the bilateral farmed fish trade between EU/EEA countries with the rest of the world, a numerical MRL of 20 µg/kg is proposed by the applicant.

A consumer exposure estimate based on the proposed MRL of 20 µg/kg praziquantel has not been provided by the applicant. In the absence of justification for a MR/TR ratio, the CVMP has selected a conservative ratio of 0.1, in order to take into account unquantified praziquantel metabolites. Based on an MRL of 20 µg/kg, a MR/TR ratio of 0.1 and a standard food basket intake of 300 g fish muscle and skin per day, a theoretical daily intake of 60 µg/person is calculated. Based on the edible portion for fish in the standard food basket, this would represent approximately 0.6% of the ADI. As total residues from both edible tissues and milk of the major species sheep at 8 hours post treatment represent less than 30% of the ADI, the establishment of an MRL of 20 µg/kg for fin fish will not impact on consumer safety. The low portion of the ADI used is considered to provide a sufficient margin of safety for any uncertainties.

From a practical perspective, taking into account species that are of commercial interest to the EU/EEA, it is noted that the mean praziquantel concentrations in rainbow trout and gilthead sea bream in muscle samples taken from treated fish at 24 hours ranged from 3–50 µg/kg. In other fish species, mean concentrations of praziquantel as high as 3610 µg/kg have been detected 24 hours following treatment in muscle.

3. 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 maximum residue limits recommended for praziquantel to other food-producing species and commodities. Taking into account the provisions laid down in Commission Regulation (EU) 2017/880, the recommendations on extrapolation are justified as follows:

Animal species/ food	**Extrapolation possible**	**Justification**

commodities	(Yes/No)	
Cattle (including milk)	No	No pharmacokinetic or residue depletion data were available for cattle. Considering that cattle is a major species, considering the absence of supporting data demonstrating similarity of metabolism in cattle and sheep, and in line with Commission Regulation (EU) 2017/880, extrapolation is not recommended.
All ruminants except cattle	Yes	No data on pharmacokinetics or residues in other ruminant species are available. However, in line with Commission Regulation (EU) 2017/880, extrapolation of the MRLs recommended for sheep, including milk, to minor ruminants can be accepted.
Pigs	No	No pharmacokinetic or residue depletion data were available for pigs. As pigs are unrelated to sheep, the species for which data are available, and in line with Commission Regulation (EU) 2017/880, MRLs cannot be extrapolated to pigs without supporting data demonstrating similarity of metabolism.
Poultry (including eggs)	No	No pharmacokinetic or residue depletion data were available for chicken. As chicken are unrelated to sheep, the species for which data are available, and in line with Commission Regulation (EU) 2017/880, MRLs cannot be extrapolated to chicken without supporting data demonstrating similarity of metabolism.
Rabbits	No	No data on pharmacokinetics or residues in rabbits are available. As rabbits are unrelated to sheep, the species for which data are available, and in line with Commission Regulation (EU) 2017/880, MRLs cannot be extrapolated to rabbits without supporting data demonstrating similarity of metabolism. In the case of extrapolation from the related minor species horses, in the absence of information on the metabolic profile in horses and rabbits, similarity in metabolism cannot be confirmed.
Honey	No	Residue depletion in honey does not occur through metabolism and consequently conclusions drawn from data in other food commodities cannot be extrapolated to honey. In the absence of honey-specific data and in line with Commission Regulation (EU) 2017/880 extrapolation to honey is not recommended.

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

Whereas:

- the toxicological ADI of 0.17 mg/kg bw (i.e. 10.2 mg/person) was established as the overall ADI

for praziquantel,

- praziquantel is rapidly and extensively metabolised in mammals,
- metabolism in fin fish is expected to be comparable to but slower than that in mammals,
- the parent compound praziquantel (sum of isomers) can apply as the marker residue as provided for in the CVMP "Note for guidance on the establishment of maximum residue limits for *Salmonidae* and other fin fish" (EMEA/CVMP/153b/97-FINAL),

and having considered that:

- the available pharmacokinetic data are heterogenous in nature such that it is not possible to reach definitive conclusions on the pharmacokinetic profile in fin fish generally,
- the ratio of praziquantel to total praziquantel metabolites is unknown in fin fish; application of a conservative MR/TR ratio of 0.1 in fin fish muscle and skin in natural proportions is appropriate,
- an analytical method for the determination of praziquantel in muscle of fin fish is available,
- extrapolation of the "no MRL required" status established for sheep to all ruminants except cattle is considered appropriate,

the Committee recommends the extension of maximum residue limits for praziquantel to muscle (muscle and skin in natural proportions) of fin fish. Furthermore, and with reference to Article 5 of Regulation (EC) No 470/2009, it is recommended that the "no MRL required" entry established in ovine species be extrapolated to other ruminants except cattle, in accordance with the following table:

Pharmaco-logically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Praziquantel	NOT APPLICABLE	All ruminants except bovine, *Equidae*	No MRL required	NOT APPLICABLE	NO ENTRY	NO ENTRY
	Praziquantel (sum of isomers)	Fin fish	20 µg/kg	Muscle and skin in natural proportions	NO ENTRY	NO ENTRY

Based on the recommended maximum residue limits, the theoretical intake of residues from fin fish tissues represents approximately 0.6% of the ADI. The worst-case consumer exposure to residues of praziquantel therefore remains that which would occur as a result of consuming foodstuffs derived from treated ruminants (total residues from edible tissues and milk of sheep at 8 hours post treatment represent less than 30% of the ADI).

5. Background information on the procedure

Submission of the dossier:	27 July 2021
Steps taken for assessment of the substance	
Application validated:	11 August 2021
Clock started:	12 August 2021
List of questions adopted:	9 December 2021
Consolidated response to list of questions submitted:	11 March 2022
Clock re-started:	14 March 2022
List of outstanding issues adopted:	12 May 2022
Consolidated response to list of outstanding issues submitted:	1 August 2022
CVMP opinion adopted:	8 September 2022