10 May 2021
EMA/CVMP/56180/2018
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Paromomycin (tissues and eggs of all food producing species)

On 12 December 2018, the European Commission adopted a Regulation[1] establishing a maximum residue limit for paromomycin in eggs, valid throughout the European Union. The maximum residue limits was based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Paromomycin is intended for use in in laying hens for the treatment of histomoniasis caused by *Histomonas meleagridis*.

Maximum residue limits had already been established for paromomycin in tissues of all food producing species[2]. Huvepharma NV submitted to the European Medicines Agency an application for the extension of maximum residue limits to eggs on 24 June 2016.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 15 February 2018 the extension of maximum residue limits for paromomycin to eggs.

Subsequently the Commission recommended on 26 July 2018 that maximum residue limits in eggs are established. This recommendation was confirmed on 16 August 2018 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 12 December 2018.

[1] Commission Implementing Regulation (EU) No 2018/1967, O.J. L 316, of 13 December 2018
[2] Commission Regulation (EU) No 37/2010, O.J. L 15, of 22 December 2009

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Summary of the scientific discussion for the establishment of MRLs

Substance name:	Paromomycin
Therapeutic class:	Anti-infectious agents / Antibiotics
Procedure number:	EMEA/V/MRL/003517/EXTN/0003
Applicant:	Huvepharma NV
Target species requested:	Chicken (eggs)
Intended therapeutic indication:	Histomoniasis caused by Histomonas meleagridis
Route(s) of administration:	Oral

1. Introduction

Paromomycin (synonym: aminosidine, CAS-No 7542-37-2) is an aminoglycoside antibiotic used for the treatment of a number of bacterial infections (colibacillosis, salmonellosis) either by parenteral administration (calves, pigs, dry cows) or by oral administration in feed or drinking water (calves, piglets, broiler chickens).

In humans paromomycin is used for the treatment of intestinal infections such as cryptosporidiosis and amoebiasis.

Paromomycin was previously assessed by the CVMP and a microbiological ADI of 25 µg/kg bw, i.e 1500 µg/person, established as the overall ADI.

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

Pharmacologically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Paromomycin	Paromomycin	All food producing species	500 µg/kg 1500 µg/kg 1500 µg/kg	Muscle Liver Kidney	For fin fish the muscle MRL relates to 'muscle and skin in natural proportions'. MRLs for liver and kidney do not apply to fin fish. Not for animals from which milk or eggs are produced for human consumption	Anti-infectious agents/Antibiotics

Huvepharma NV submitted an application for the establishment of a maximum residue limit in chicken eggs to the European Medicines Agency on 24 June 2016.

The proposed indication in laying hens is histomoniasis caused by *Histomonas meleagridis*. The recommended dose is between 12.5 and 25 mg/kg bw per day in feed for 10 days.

2. Scientific risk assessment

2.1. Safety assessment

The Committee for Medicinal Products for Veterinary Use (CVMP) previously assessed the consumer safety of paromomycin and established a microbiological ADI of 25 µg/kg bw, i.e. 1500 µg/person, as the overall ADI, based on potential effects on the gastrointestinal colonisation barrier.

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 original pharmacokinetic studies in the target species were provided for this application, which instead made reference to published literature and, in particular, the European Medicines Agency (EMA) summary report for paromomycin, dated January 2000 (EMEA/MRL/718/99-FINAL).

In its Summary Report the CVMP stated that after oral administration paromomycin sulfate is poorly absorbed from the gastrointestinal tract and most of the dose is eliminated unchanged in the faeces. After parenteral administration, accumulation occurs in the renal cortex and the cochlea, and excretion is almost exclusively in the urine as unchanged drug.

Pharmacokinetic studies, compliant with OECD GLP guidelines, were performed in rabbits, poultry, bovine and porcine species. No substantial differences between species were observed. Like other aminoglycosides, paromomycin is poorly absorbed from the gastrointestinal tract.

In chickens, a total of 250 young birds received paromomycin sulfate via gastric probe, equivalent to 43 mg/kg bw of paromomycin at 1, 3, 5, 8 and 15 days of life. Blood samples were obtained 1, 2, 3, 4, 5, 6, 12 and 24 hours post-treatment and were analysed by microbiological assay. The results demonstrated that paromomycin was absorbed to a small extent; concentrations were higher in younger chickens compared to older chickens.

No data were provided on the likely metabolites that could be found in eggs, but since it has already been established that the majority of a dose of paromomycin is excreted unchanged, this is can be accepted.

Based on the physical properties of aminoglycosides (cationic, with a high degree of polarity), birds are most likely to also eliminate orally-administered aminoglycosides in the faeces, although data specific to birds are lacking. When aminoglycosides are administered systemically they are far more bioavailable than when given orally; therefore, residues are more likely to be found in eggs. When administered to laying hens by the intramuscular or subcutaneous routes, both gentamicin and dihydrostreptomycin were found in egg yolk and albumen, with residues persisting for longer periods in the yolk. Probably because of the poor gastrointestinal absorption of aminoglycosides, no residues were found in eggs following the oral administration of dihydrostreptomycin, neomycin, apramycin or

kanamycin, except in the latter case in yolk, but this only when extremely high concentrations were used.

The rate of absorption may be increased in the presence of infections of the digestive tract which may result in compromise of the normal epithelial barrier.

2.2.2. Residue depletion studies

No radiolabelled study was provided.

A GLP compliant residues depletion study in eggs of two groups of chickens treated with daily doses of 12.5 (group 1) and 25.0 (group 2) mg paromomycin/kg bw for 10 consecutive days was conducted. Ten eggs per group were collected daily for the ten days of treatment and for 16 days after the end of treatment. No residues findings above the limit of quantification of the analytical method used (100 µg/kg) are reported in any samples taken.

No data on residues depletion of paromomycin in eggs from other poultry species than chicken were provided.

Selection of marker residue and ratio of marker to total residues

Paromomycin is hardly metabolised or not metabolised at all and therefore the parent compound is considered a suitable maker residue. The ratio of marker to total residues is considered to be 1.

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

An LC-MS/MS method for the analysis of paromomycin in eggs was presented in an internationally acceptable format and validated to a set of parameters which are largely in compliance with the requirements as defined in Volume 8 of the Notice to Applicants (2005) and VICH GL49 (2012). The calculated LOQ was 85 µg/kg but as accuracy and precision were not demonstrated at this level, in accordance with VICH GL49, the accepted LOQ is 100 µg/kg.

The relevant European Reference laboratory has reviewed the proposed analytical method and is in agreement with the above conclusions. However, the point was made that the value of 100 µg/kg, considered by CVMP as the LOQ, is not fully representative of the capability of the analytical method (which is, in fact, more sensitive) and that, strictly speaking, this value might be better termed the 'limit of determination at the lowest calibration point'.

2.2.5. Findings of EU or international scientific bodies

EFSA's FEEDAP Panel adopted an opinion[3], in May 2009, relating to the safety and efficacy of paromomycin sulphate when used as a feed additive for turkeys. EFSA retained the tissue MRLs previously recommended by CVMP and in addition retained a provisional value of 1500 µg/kg for skin/fat.

[3] EFSA Journal (2009) 1095, 1-22. Scientific Opinion of the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) on a request from the European Commission on the preliminary evaluation of the safety and efficacy of paromomycin sulphate for turkeys for fattening and turkeys reared for breeding.

3. Risk management considerations

3.1. Availability of alternative medicines and other legitimate factors

Availability of alternative medicines

Availability of veterinary medicines for laying hens is very limited. The lack of veterinary medicines for this category of animals was taken into account by the CVMP when considering the recommendation for the establishment of a MRL for paromomycin in eggs. In total, there are only 12 antimicrobial substances with MRLs established for eggs in the EU. Of these, none are currently authorised for the treatment of histomoniasis in laying hens.

Histomoniasis is a protozoal disease of poultry which predisposes to secondary infections and, if inadequately controlled, impacts seriously on animal health and welfare; therefore it is important to encourage the availability of treatments for this disease.

There is currently no MRL for paromomycin in milk. There are seven alternative aminoglycoside antibiotics with established MRLs in milk (streptomycin, dihydrostreptomycin, framycetin, gentamicin, kanamycin, neomycin, and spectinomycin) which would have a similar spectrum of antibacterial activity to paromomycin.

It is acknowledged that there are no antimicrobial substances with MRLs in honey. The most significant bacterial diseases of honey bees are American Foulbrood and European Foulbrood. Streptomycin has been used to treat bee hives for these conditions, but is not currently authorised for this use in the EU.

Technological aspects of feed and food production

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

Conditions of use

In the absence of MRLs for milk, the use of paromomycin is restricted to animals not producing milk for human consumption.

The need for a restriction to oral use was considered, since it is known that pharmacokinetics are very different after parenteral administration compared to after oral administration; however, if a numerical MRL is set, withdrawal periods will be derived on a product basis using data generated using the relevant route of administration, so this restriction would not be required.

It is noted that histomoniasis, the indication for which paromomycin is intended, causes inflammation in the gastrointestinal tract, which may lead to a higher oral systemic bioavailability due to loss of integrity of the gastrointestinal barrier. This may lead to higher residues than indicated from data derived following administration to healthy animals.

Paromomycin has no known use as a biocide or plant protection product; although MRLs have been evaluated in relation to the use of paromomycin as a feed-additive; there are no feed-additive products currently authorised.

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

3.2. Elaboration of MRLs

Based on the residue depletion data available and the accepted LOQ of the analytical method (100 µg/kg), the MRL can be set at twice the LOQ, in line with Volume 8 of The rules governing medicinal products in the European Union. An MRL of 200 µg/kg in eggs is therefore considered acceptable.

Calculation of theoretical daily intake of residues

Edible tissue or products	Daily consumption (kg)	MRL proposal (µg/kg)	Ratio of the marker/total residue	Amount per edible tissue or product (µg)
Muscle	0.30	500	1	150
Liver	0.10	1500	1	150
Kidney Mammals Poultry	 0.05 0.01	 1500	 1	 75* 15
Eggs	0.10	200	1	20
			TMDI:	**395**

*worst case scenario. There are no MRLs set for paromomycin in fat.

Based on the above figures the theoretical maximum daily intake (TMDI) represents 26.34% of the ADI (of 1500 µg/person).

3.3. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EC) No 470/2009 and in line with the criteria laid down in Regulation (EU) 2017/880, as MRLs can be recommended for paromomycin in chicken eggs, the CVMP has considered the possibility of extrapolating its recommendation to other food producing species and commodities. An extrapolation to poultry eggs is recommended as the marker residue (parent molecule) is likely to be present in eggs from other poultry species. Furthermore, the analytical method can also be assumed to be basically applicable to eggs of other poultry species.

Extrapolation to honey and milk was also considered, but could not be recommended based on the available data.

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

Whereas:

- the microbiological ADI of 25 µg/kg bw (i.e.1500 µg/person) was established as the overall ADI for paromomycin,
- the parent compound was retained as the marker residue,
- the ratio of marker to total residues was 1 in eggs,
- a validated analytical method for the monitoring of residues of paromomycin in chicken eggs is available and can be assumed to be applicable also to eggs of other poultry species,
- extrapolation of the maximum residue limit recommended for chicken eggs to eggs of other poultry species is considered appropriate;

The CVMP recommends the establishment of a maximum residue limit for paromomycin in chicken eggs. Furthermore, with reference to Article 5 of Regulation (EC) No 470/2009 and in line with the criteria laid down in Regulation (EU) 2017/880, the Committee agreed to extrapolate the conclusions to all poultry eggs. Therefore, the Committee recommends by consensus the amendment of the entry for paromomycin in table 1 (Allowed substances) of the Annex to Regulation (EU) No 37/2010 as follows:

Pharmaco-logically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Paromomycin	Paromomycin	All food producing species	500 µg/kg 1500 µg/kg 1500 µg/kg 200 µg/kg	Muscle Liver Kidney Eggs	For fin fish the muscle MRL relates to 'muscle and skin in natural proportions'. MRLs for liver and kidney do not apply to fin fish. Not for use in animals from which milk is produced for human consumption.	Anti-infectious agents/Anti-biotics

Based on the MRLs for edible tissues and eggs, the theoretical maximum daily intake (TMDI) will remain below 27% of the ADI.

4. Background information on the procedure

Submission of the dossier	24 June 2016
Steps taken for assessment of the substance	
Application validated:	13 July 2016
Clock started:	14 July 2016
List of questions adopted:	10 November 2016
Consolidated response to list of questions submitted:	5 July 2017
Clock re-started:	10 July 2017
List of outstanding issues adopted:	7 September 2017
Consolidated response to list of questions submitted:	15 January 2018
Clock re-started:	17 January 2018
CVMP opinion adopted:	15 February 2018