European Food Safety Authority

The EFSA Journal (2009) 1095, 1-22

SCIENTIFIC OPINION

Preliminary evaluation of the safety and efficacy of paromomycin sulphate for turkeys for fattening and turkeys reared for breeding[1]

Scientific Opinion of the Panel on Additives and Products or Substances used in Animal Feed

(Question No EFSA-Q-2009-00445)

Adopted on 13 May 2009

PANEL MEMBERS

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SUMMARY

Following a request from the European Commission (Article 15 of Regulation (EC) No 1831/2003), the European Food Safety Authority (EFSA) was asked to deliver a preliminary evaluation of the safety and efficacy of paromomycin sulphate when used as feed additive under the category coccidiostats/histomonostats.

HistoBloc® contains 8 % paromomycin sulphate, an aminoglycoside antibiotic, produced by fermentation of *Streptomyces chrestomyceticus*. It is applied to prevent histomoniasis in turkeys for fattening and turkeys reared for breeding at concentrations between 100 and 400 mg kg^{-1} complete feed.

The safety for the target animal of paromomycin sulphate from histoBloc® at the highest proposed dose (400 mg kg^{-1} diet) could not be established due to the absence of data.

Paromomycin sulphate shows an antimicrobial effect on susceptible bacterial strains at levels considerably lower than those proposed for feed use. Even at the lowest proposed feed concentration (100 mg kg^{-1} diet), it selects for resistance and cross-resistances at high frequency against a variety of other aminoglycosides among intestinal bacteria. As aminoglycoside antibiotics are used in human and veterinary medicine, serious consequences

[1] For citation purposes: 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. *The EFSA Journal* (2009) 1095, 1-22

for antibiotic therapy in humans and animals can be anticipated following the use of paramomycine as a feed additive.

Data on paromomycin sulphate from histoBloc® concerning metabolism and toxicology were not supplied. The Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) follows therefore in these aspects the Summary Report of EMEA/CVMP on paromomycin sulphate.

The limited data available on paromomycin sulphate metabolism indicate that (i) orally administered paromomycin sulphate is absorbed to a very limited extent, (ii) negligible biotransformation occurs following absorption, (iii) no accumulation in tissues occurs (with the exception of the kidney) and (iv) paromomycin sulphate constitutes most of the residues in tissues. Paromomycin sulphate is the marker residue. No conclusions on the similarity of the metabolic fate of paromomycin sulphate in turkeys and laboratory animals can be drawn.

Paromomycin sulphate has a very low oral acute toxicity, it is not mutagenic, genotoxic, carcinogenic or teratogenic. Oral chronic toxicity in dogs resulted in the lowest NOEL of approximately 3.4 mg paromomycin sulphate kg^{-1} bw, leading to a toxicological ADI of 0.034 mg kg^{-1} bw.

A residue study with histoBloc® in turkeys, at the highest dose proposed for use (400 mg kg^{-1} feed), indicates higher concentrations of paromomycin sulphate in kidney, followed by muscle and liver. No measurement was performed in skin/fat. The FEEDAP Panel estimates consumer exposure after a ten-day withdrawal, extrapolating skin/fat data from a study in chickens, to 0.214 mg day^{-1}, representing about 10 % of the toxicological ADI.

As MRLs, the FEEDAP Panel retains the EMEA/CVMP values for liver, kidney and muscle (1.5, 1.5 and 0.5 mg kg^{-1}, respectively) and adds the provisional value of 1.5 mg kg^{-1} for skin/fat. The corresponding consumer exposure would represent 28 % of the toxicological ADI. A withdrawal time of ten days is proposed for turkeys for fattening.

According to the applicant, histoBloc® is harmful by inhalation and if swallowed. It is also irritating to the eyes. Other issues, such as the potential for sensitisation, have not been considered.

Preliminary calculations indicate that the trigger values for soil and groundwater would be exceeded and thus a Phase II assessment is needed. In the absence of any experimental data on the fate and ecotoxicity of paromomycin sulphate, the FEEDAP Panel cannot conclude on the safety of histoBloc® for the environment.

Due to the complete lack of data under practical conditions and despite the probable efficacy of paromomycin sulphate against histomoniasis in turkeys, a conclusion on the efficacy of histoBloc® under field conditions, particularly on the effective dose, is not possible.

Recommendations have been made concerning the protection of the user and post-market monitoring.

Key words: coccidiostats and histomonostats, paromomycin sulphate, histoBloc®, antibiotic, aminoglycoside, histomoniasis, turkey, bacterial resistance, cross-resistance, safety, efficacy, MRLs

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BACKGROUND AS PROVIDED BY EC

Council and Parliament Regulation (EC) No 1831/2003 foresees in Article 15 the possibility that the Commission may provisionally authorise, for a maximum period of five years, an additive to ensure the protection of animal welfare.

Huvepharma Company provided a dossier on paromomycin sulphate (CAS 1263-89-4), for use as feed additive to prevent histomoniasis (blackhead disease) following the conditions proposed in the dossier. Taking into account the urgency of this matter for turkey farming and the preparation of a dossier for a full authorisation of the molecule could take up to five years, the Commission accepted to consider the dossier.

TERMS OF REFERENCE AS PROVIDED BY EC

The Commission asks the European Food Safety Authority to make a preliminary evaluation of the safety and efficacy of paromomycin sulphate (CAS 1263-89-4), and its metabolites when it is used as feed additive for animal nutrition following the conditions in the dossier.

ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank the members of the Working Group on Coccidiostats and Histomonostats as well as Reinhard Kroker for the preparation of this opinion.

Table 1. **Register entry as proposed by the applicant**

Additive	Paromomycin sulphate
Registration number/EC No/No (if appropriate)	
Category of additive	Coccidiostats and histomonostats
Functional group of additive	

Description			
Composition, description	**Chemical formula**	**Purity criteria (if appropriate)**	**Method of analysis (if appropriate)**
Additive composition Paromomycin sulphate 8.0 mg/g Mineral carrier	$C_{23}H_{45}N_5O_{14}S.H_2SO_4$ sulphate of (2R, 3S, 4R,5R, 6S) – 5 – amino – 6 [(1R, 2S, 3S, 4R, 6S) – 4, 6 diamino – 2 - (2S,3R, 4R, 5R) – 4 - [(2R, R, 4R, 5R, 6S) – 3 – amino – 6-(aminomethyl) – 4, 5 – dihydroxy – oxan – 2 – yl_oxy – 3 – hydroxyl – 5 – (hydroxymethyl) oxolan – 2 - yl] oxy – 3 - hydroxycyclohexyl] oxy – 2 – (hydroxymethyl) oxane – 3, 4 – diol Cas N° 1263-89-4		

Trade name (if appropriate)	Histobloc
Name of the holder of authorisation (if appropriate)	Huvepharma NV

Conditions of use				
Species or category of animal	**Maximum Age**	**Minimum content**	**Maximum content**	**Withdrawal period (if appropriate)**
		mg kg^{-1} of complete feedingstuffs		
turkeys for fattening Turkeys reared for breeding	12 weeks 16 weeks	100 mg/kg	400 mg/kg	14 days

Other provisions and additional requirements for the labelling	
Specific conditions or restrictions for use (if appropriate)	For animal treatment only. For use in turkeys. This histomonostat should not be mixed or used simultaneously with any other medicinal product having a similar effect. Can be mixed with anticoccidials. Keep out of reach of children. Expiry date is 2 years from the date of manufacture. The product will remain stable in the finished feedingstuffs for 3 months.

Specific conditions or restrictions for handling (if appropriate)	Harmful by inhalation and if swallowed. Irritating to eyes. When using do not eat, drink or smoke. Do not breathe dust. Avoid contact with eyes. In case of contact with eyes wash with plenty of water. Wear suitable protective clothing, gloves and eye/face protection. In case of insufficient ventilation, wear suitable respiratory equipment. In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible). Do not empty into drains. This material and its container must be disposed of in a safe way.
Post market monitoring (if appropriate)	
Specific conditions for use in complementary feedingstuffs (if appropriate)	

Maximum Residue Limit (MRL) (if appropriate)			
Marker residue	**Species or category of animal**	**Target tissue(s) or food products**	**Maximum content in tissues**
paromomycin	all food producing species	muscle liver kidney	500 µg/g 1500 µg/kg 1500 µg/kg

ASSESSMENT

1. Introduction

Paromomycin sulphate is a broad-spectrum aminoglycoside antibiotic produced by fermentation of *Streptomyces chrestomyceticus*, used as a veterinary drug (under different trade names) for the treatment of bacterial infections in different species, including poultry. It exhibits also preventive effects against histomoniasis (blackhead disease), a debilitating disease in turkeys.

Due to the lack of histomonostats authorised as feed additives in Europe, and the urgency of this matter for turkey farming, the Commission has asked the European Food Safety Authority (EFSA), in the framework of Article 15 of Regulation (EC) No 1831/2003, to make a preliminary evaluation of the safety and efficacy of paromomycin sulphate when used as feed additive under the category coccidiostats and histomonostats, on the basis of the dossier prepared by the applicant.

Paromomycin sulphate is the active substance of the additive histoBloc 80® MicroGranulate (histoBloc®) for which an authorisation is seeked.

Paromomycin sulphate has been assessed by EMEA/CVMP several times (EMEA/CVMP, 1996, 2000, 2002) and is authorised as a veterinary drug for parenteral (calf, pig and dry cow) or oral administration through feed and water (calf, piglet and chicken). MRLs of 500 μg kg^{-1} for muscle and 1500 μg kg^{-1} for liver and kidney for all species, including poultry, have been set and are enforced.

In human therapy, paromomycin sulphate is used to treat some (intestinal) parasitoses (amoebiasis, giardiasis, leishmaniosis).

2. Characterisation

2.1. Identity of the additive

HistoBloc® contains 80 g paromomycin sulphate kg^{-1}. It is composed of 800 to 950 g dried fermentation product kg^{-1}, 10 to 30 g pre-gelatinised starch kg^{-1} as granulation agent and calcium carbonate up to 1 kg.

The results of the analysis of five batches[2] of histoBloc® indicate paromomycin sulphate concentrations of 80, 80, 83, 82 and 84 g kg^{-1} (validated microbiological method), which comply with the specification given by the applicant of 76 to 84 g kg^{-1} (5 % variation).

The additive is a beige brown granulate. The study of the same five batches[3] showed that more than 99 % of the particles was < 800 μm, and less than 1.5 % was < 100 μm. Although this might indicate a dusting potential, no measurements have been performed for the critical values of 100 μm (inhalable fraction), 50 and 10 μm (respirable fraction) and/or the dusting properties.

[2] Technical dossier/Section II/Reference II.1
[3] Technical dossier/Section II/Reference II.1

2.2. Characterisation of the active substance

Paromomycin sulphate is produced by a fermentation process with the strain *Streptomyces chrestomyceticus* (NBIMCC 3383, certificate of strain deposition not provided). The chemical name (IUPAC) is (2R,3S,4R,5R,6S)-5-amino-6-[(1R,2R,3S,4R,6S)-4,6-diamino-2-[(2S,3R,4S,5R)-4-[(2R,3R,4R,5S,6S)-3-amino-6-(aminomethyl)-4,5-dihydroxyoxan-2-yl]oxy-3-hydroxy-5-(hydroxymethyl)oxolan-2-yl]oxy-3-hydroxycyclohexyl]oxy-2-(hydroxymethyl)oxane-3,4-diol sulphate. The structural formula is $C_{23}H_{45}N_5O_{14}.xH_2SO_4$, CAS number [1263-89-4]. The molecular weight of paromomycin sulphate is 615.

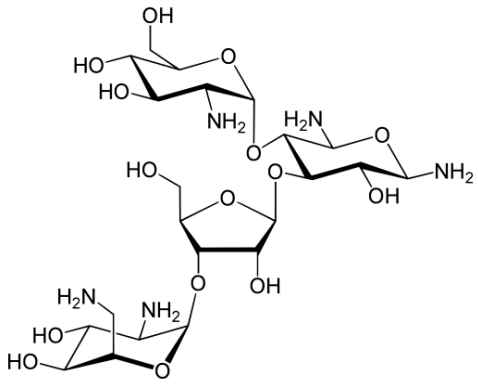

Figure 1. **Structural formula of paromomycin sulphate**

Characterisation by IR spectroscopy, NMR analysis and X-ray diffraction is described.

The analysis of heavy metals in five batches of histoBloc® indicates values of 0.10 to 0.14 mg lead $kg^{-1}$and 0.089 to 0.092 mg cadmium kg^{-1}, and 0.21 to 0.51 mg arsenic kg^{-1}. The analysis of the same batches indicates the absence of *Salmonella*, *E.coli* and *Staphylococcus aureus.* Total bacteria are < $2x10^3$ CFU g^{-1}, moulds < 10^2 CFU g^{-1}, Enterobacteriaceae and other Gram-negative bacteria < 10 CFU g^{-1}.

Mycotoxins (aflatoxin, deoxynivalenol, zearalenone and ochratoxin) were not detected in the five batches (limits of detection: 0.5, 100, 5 and 0.3 µg kg^{-1}, respectively). No living cells of the production strain were detected in the paromomycin sulphate dried fermentation product (analysis of three batches).

2.3. Manufacturing process

Detailed information is given on the manufacturing process of the paromomycin sulphate dried fermentation product.

The manufacturing process of histoBloc® is described, including standardisation of the dried fermentation product to a paromomycin sulphate concentration of 80 g kg^{-1} by addition of calcium carbonate, and the granulation of the standardised product using aqueous pre-gelatinised starch.

2.4. Physico-chemical and technological properties of the additive

2.4.1. Shelf life of the additive

Three batches of histoBloc® kept in their original paper/polyethylene bags have been submitted to two different storage conditions: either normal 25 °C/RH 60 % for 24 months or accelerated 40 °C/RH 75 % for six months. A 6 % and 4 % decrease of the initial concentration of paromomycin sulphate measured with a validated microbiological method (83 to 78 g kg^{-1}) was observed for the three batches, after six months under accelerated conditions or after 18 months when stored under normal conditions, respectively. The applicant proposed a shelf life of 24 months.

2.4.2. Stability in premixtures and feedingstuffs

No data on the stability of histoBloc® in premixtures were provided.

Four batches of feedingstuffs for turkeys have been supplemented with histoBloc® at two levels corresponding to 100 and 400 mg paromomycin sulphate kg^{-1} feed. Samples were stored either at 25 °C for three months or 40 °C for four weeks. Decreases of the concentrations of paromomycin sulphate of 14 and 15 % were measured in the samples (100 and 400 mg kg^{-1} respectively) kept under accelerated conditions, but only 6 and 7 % in normal conditions.

Stability during the pelleting process was evaluated at 65, 75 and 85 °C in turkey feeds supplemented with histoBloc® at paromomycin sulphate concentrations of 100, 200 and 400 mg kg^{-1}. No appreciable decrease of paromomycin sulphate concentration was observed, whatever the treatment.

2.4.3. Homogeneity

The homogeneity of the additive mixed in turkey feedingstuffs (four batches, 0, 100, 200 and 400 mg paromomycin sulphate kg^{-1}) has been tested based on the analysis of paromomycin sulphate in six samples of each batch. The coefficients of variations were 6, 7 and 8 % for 100, 200 and 400 mg paromomycin sulphate kg^{-1}, respectively.

2.5. Conditions of use

HistoBloc® is proposed for use as feed additive for the control of *Histomonas meleagridis* in turkeys. The minimum dose is 100 mg and the maximum dose 400 mg paromomycin sulphate kg^{-1} feed.

3. Safety

3.1. Safety for the target species

3.1.1. Tolerance studies

The dossier provides information on a tolerance study on turkeys started in 2008, but only the protocol of the study was submitted.[4] The protocol is as follows:

Four treatment groups (one pen with 21 male and 21 female turkeys (breed: BIG6 BUT) per treatment) should be fed the same basal diet containing 0, 400 (highest use dose), 800 and 4000 mg paromomycin sulphate kg^{-1} (tenfold the highest use dose). The diets (starter for weeks 1–4, grower I for weeks 5–8, grower II for weeks 9–12 and finisher for weeks 13–16) should consist mainly of wheat, soybean meal and corn. Each batch was foreseen for analytical control of paromomycin sulphate content.

Health status should be checked daily, the zootechnical parameters would be recorded until week 12 in weekly intervals, afterwards biweekly. At the end of the study, blood samples (six males and six females per treatment group) should be examined for haematology and blood biochemistry. Macroscopic postmortem examination should be performed on ten male and ten female turkeys per treatment. For histological examination, one ovary, one kidney, liver and spleen should be collected from three female turkeys per treatment.

The applicant noted that the 'interim results after five weeks show that no negative effects were observed even at the highest tested concentration.'

3.1.2. Microbiological safety of the additive

MIC-values of paromomycin sulphate against susceptible and resistant strains

The MICs of paromomycin sulphate have been determined[5] against two strains of *Staphylococcus aureus,* 14 strains of *Escherichia coli*, 12 strains of *Pseudomonas aeruginosa*, two strains of *Klebsiella pneumonia* and three *Serratia* sp.. The lowest MICs for sensitive strains varied between 0.78 (*S. aureus*) and 12.5 $\mu g\ mL^{-1}$ (*P. aeruginosa*), while the resistant strains typically had MICs of $> 100\ \mu g\ mL^{-1}$.

The MIC ranges of paromomycin sulphate[6] against human derived *Salmonella* Typhimurium (117 isolates) and *S.* Enteritidis (39 isolates) were generally in the range of 0.5–4 $\mu g\ mL^{-1}$, while the MICs for resistant isolates (mostly *S.* Typhimurium) were $> 32\ \mu g\ mL^{-1}$.

Selection of bacterial cross-resistance to aminoglycoside antibiotics

A study[7] was performed with turkeys receiving feed supplemented with 100 mg kg^{-1} paromomycin sulphate for 17 weeks to assess the development of resistance in intestinal *E. coli* and *Enterococcus* isolates and in zoonotic *Staphylococcus aureus.* The trial was done in farm conditions with 12 experimental and untreated control groups (54 460 treated vs. 44 165 control turkeys). Droppings were collected monthly until two months after the end of the supplementation period, the total number of samples collected being 168. The randomly

[4] Technical dossier/Section III/Reference 2
[5] Technical dossier/Annex III/Reference 4
[6] Technical dosseier/Annex III/Reference 5
[7] Technical dossier/Annex III/Reference 14

picked bacterial isolates were tested for resistance, in addition to common aminoglycosides, against amoxicillin, tetracycline, cefotaxime, amoxicillin-clavulanic acid, cefalexin, chloramphenicol, nalidixic acid, ciprofloxacin, trimethoprim, vancomycin, teicoplanin, erythromycin, ampicillin, lincomycin, pristinamycin, penicillin, and cefoxitine. Both the agar diffusion and agar dilution methods were used.

According to the results, *E. coli* strains isolated from treated turkeys (12 randomly picked isolates per treatment per time point) were significantly ($P < 0.05$) more often resistant to paromomycin sulphate (MIC > 64 µg mL^{-1}), neomycin and kanamycin than those isolated from controls, and this effect was still present at one month after the supplementation had ceased. The effect on *E. faecium* was transient (occurring at two and three months) and limited to kanamycin and streptomycin resistance (determined by agar diffusion method; no data reported on paromomycin sulphate). While all the nine *Staphylococcus aureus* isolates obtained from unsupplemented birds were sensitive to all aminoglycosides, the isolates from treated birds (altogether 15 isolates, with only five from the actual supplementation period) were frequently resistant to paromomycin sulphate (11/14, MIC > 64 µg mL^{-1}), kanamycin (8/15), tobramycin (9/15), amikacin (4/15) and neomycin (6/15) (the four latter antibiotics being tested with the agar diffusion method).

No selection for cross-resistance against other antibiotics, except aminoglycosides, was observed.

The effects on pathogen shedding

The applicant has provided a protocol for a shedding trial on *Salmonella* Enteritidis and campylobacter, but the results were not submitted.

3.1.3. Conclusion on safety for the target species

Conclusions on the safety of paromomycin sulphate when fed continuously for 16 weeks at 400 mg kg^{-1} diet to turkeys cannot be drawn due to the lack of data. Even if the data of the scheduled tolerance study are made available, conclusions on the zootechnical parameters will be limited because no replicates per treatment are foreseen.

An extrapolation on the safety of 400 mg kg^{-1} diet from the limited data submitted after administration of 100 mg paromomycin kg^{-1} diet to turkeys is not possible.

Based on the MIC data, paromomycin sulphate clearly has an antimicrobial effect on susceptible bacterial strains at levels considerably lower than those proposed for feed use. It has also been demonstrated that paromomycin sulphate, even at the lowest proposed feed concentration, selects for resistance and cross-resistances against a variety of other aminoglycosides among intestinal bacteria. Aminoglycoside antibiotics are used in human and veterinary medicine. Serious consequences for antibiotic therapy in humans and animals cannot be excluded.

3.2. Safety for the consumer

3.2.1. Metabolic and residue studies

3.2.1.1. Metabolism

No metabolic study of paromomycin sulphate from histoBloc® has been provided.

Only limited information is available from the summary reports of EMEA/CVMP assessment of paromomycin sulphate (EMEA/CVMP, 1996; EMEA/CVMP, 2000). The main conclusions are the following: i) after oral administration, paromomycin sulphate, like other aminoglycosides, is poorly absorbed from the intestinal tract and most of the dose is eliminated unchanged in faeces, ii) paromomycin sulphate undergoes negligible biotransformation when administered parenterally, the parent compound being consistently the main compound of the total residues in both urine and faeces, iii) paromomycin sulphate does not accumulate in tissues during treatment, except for the renal cortex, iv) paromomycin sulphate is the marker residue, v) pharmacokinetic studies performed in poultry, rabbits, bovine and pigs indicate no substantial differences between species.

The FEEDAP Panel notes that no data is given on the comparative paromomycin sulphate metabolic fate in poultry and laboratory animals.

3.2.1.2. Residues

A GLP study of the residues of paromomycin sulphate in turkey tissues following the administration of histoBloc® has been carried out.[8] Six groups of three male plus three female one-day-old turkeys received a starter feed supplemented with histoBloc® and a coccidiostat until day 21, then a starter/grower feed containing histoBloc® at the maximum dose proposed for use, i.e. 400 mg paromomycin sulphate kg^{-1} (dosage analytically controlled), from day 21 to day 112 (16 weeks). The animal groups were slaughtered after 10-, 20-, 30-, 40-, 50- and 60-day withdrawals, and liver, kidney, muscle and skin/fat (in natural proportion) were sampled. A LC-MS analytical technique was used to determine paromomycin sulphate residues in tissues, with LOQs of 0.6 mg kg^{-1} for liver and kidney, respectively, and 0.2 mg kg^{-1} for muscle. The corresponding LODs were 0.14, 0.14 and 0.10 mg kg^{-1}, respectively. The results are summarised in Table 2.

Table 2. **Paromomycin sulphate residues in tissues (mg kg-1) of turkeys fed histoBloc® at the maximum dose proposed for use (400 mg paromomycin sulphate kg^{-1} feed) for 16 weeks followed by a withdrawal period**

Withdrawal time (days)	Liver	Kidney	Muscle
10	<LOD[1]	0.392 ± 0.003	0.154 ± 0.009
20	<LOD	0.390 ± 0.004	0.170 ± 0.024
30	<LOD	0.390 ± 0.003	0.156 ± 0.016
40	<LOD	0.390 ± 0.002	0.149 ± 0.002
50	<LOD[2]	0.391 ± 0.005	0.152 ± 0.004
60	<LOD	0.389 ± 0.003	0.147 ± 0.024[3]

[1] LOD = 0.14 mg paromomycin sulphate kg^{-1}
[2] Two values above the LOD (0.142 and 0.153 mg kg^{-1})
[3] One value < LOD

Whereas the tissue has been sampled, paromomycin sulphate residues have not been measured in the skin/fat and no reason is given for this absence. The highest levels of residues have been found in the kidneys, which is consistent with the scarce data on the metabolic fate of paromomycin sulphate (see Section 3.2.1.1.). All analytical results are below the LOQ of the analytical method. No depletion of residues occurs between 10- and 60-day withdrawals. It must be noted that the standard deviations measured are generally very narrow, which is in contrast with the considerable inter-individual variations usually

[8] Technical dossier/Section III/Reference 17

observed for traces amounts of residues in tissues or with the increasing variability where the values are comprised between the LOQ and LOD. The fact that the standard deviations of paromomycin sulphate residue levels measured in the kidneys and muscles of six individual animals are much lower than those from the inter- and intra-day repeated analyses of single individual samples appears inconsistent.

Only the summary of a residue study performed in poultry (chickens) following the administration of paromomycin sulphate applied as veterinary drug was available (EMEA/CVMP, 1996). The birds received for five consecutive days medicated feed containing 280 mg paromomycin sulphate kg^{-1} then where slaughtered after 0-, 2-, 7- and 14-day withdrawals. Paromomycin sulphate residues were measured using an analytical method with a LOQ of 0.1 mg kg^{-1} for all tissues. Residues in liver and muscle were below the LOQ at any sampling time. In kidney, residues of 2.6 mg kg^{-1} were measured at a 0-day withdrawal and were not detectable after a four-day withdrawal. Residue values in skin/fat amounted to 1.4 and 0.5 mg kg^{-1} after 0- and 7-day withdrawals, respectively, and were < LOQ after14 days.

This study indicates that, whereas the dose administered to chickens is around 2/3 that received by turkeys, and the duration of the treatment much shorter (five instead of 112 days), considerable amounts of residues of paromomycin sulphate are still present in the skin/fat after a seven-day withdrawal. Considering the physiologic/metabolic similarity of chickens and turkeys, it is likely that significant amounts of paromomycin sulphate would be present in turkey skin/fat also.

3.2.1.3. Conclusions on metabolism and residue studies

The limited data available indicates that (i) orally administered paromomycin sulphate is absorbed at a very limited extent, (ii) negligible biotransformation occurs following absorption, (iii) no accumulation in tissues occurs (with the exception of the kidney) and (iv) paromomycin sulphate constitutes most of the residues in tissues. Paromomycin sulphate is the marker residue. No evidence is given that the metabolic fate of paromomycin sulphate in turkeys is similar to/different from that in laboratory animals.

A residue study of paromomycin sulphate from histoBloc® in turkeys, at the highest dose proposed for use (400 mg kg^{-1} feed) indicates that the highest concentrations occur in kidney, followed by muscle and liver. No measurement was performed in skin/fat. The long and constant persistence of paromomycin sulphate residues in kidney and muscle (60 days) is in contrast with the relatively rapid decline observed in chickens. Moreover, flaws have been noted in the analysis of paromomycin sulphate residues in turkey tissues.

3.2.2. Toxicological studies

No studies on the toxicity of paromomycin sulphate from histoBloc® have been submitted. The applicant mainly refers to the EMEA/CVMP summary report (2000) on paromomycin sulphate. A search in PubMed database (search terms: paromomycin sulphate or aminosidine toxicity, limited to the last ten years) did not result in more recent findings relevant to consumer safety. The FEEDAP Panel consequently refers to the main conclusion of the EMEA/CVMP Summary Report.

Paromomycin sulphate is not mutagenic and not genotoxic. It shows a very low acute toxicity after oral administration. No repeated dose studies using the oral route were available. In several parenteral repeated dose studies (in rats, mice, rabbits and cats), no NOEL could be determined. Fertility and developmental studies (on mice, rats and rabbits, by parenteral

route) did not result in findings of concern. Chronic/carcinogenicity toxicity studies on rats (oral administration) did not show evidence of treatment-related increases in neoplastic or non-neoplastic alterations, the NOEL being approximately 78.5 mg kg^{-1} bw. A chronic toxicity study in dogs (oral administration) resulted in a NOEL of approximately 3.4 mg kg^{-1} bw.

3.2.3. Assessment of consumer safety

3.2.3.1. Proposal for an ADI

EMEA/CVMP (2000) derived a toxicological ADI from the chronic dog study of 34 μg kg^{-1} bw. The FEEDAP Panel notes that as long as the similarity of the metabolic fate and residues of paromomycin sulphate in turkey and laboratory animals is not established, there is no assurance that the consumer would be exposed to the same metabolites assessed in the toxicological studies. Consequently, no ADI can be applied. However, considering that paromomycin sulphate is absorbed at a very low extent and it is not metabolised significantly, it is likely that the laboratory animals and the consumer would be exposed predominantly to the parent compound.

EMEA/CVMP (2000) established for further safety considerations a microbiological ADI of 25 μg kg^{-1} bw, lower than the toxicological ADI.

3.2.3.2. Consumer exposure

Only paromomycin sulphate residues have been identified and measured in turkey tissues, with the exception of skin/fat. The total residues derived from paromomycin sulphate, which must be considered at first of possible toxicological concern, have not been identified or measured in tissues. As the ratio paromomycin sulphate vs. total residues cannot be established for any tissues, whatever the withdrawal period, the back-calculation of total residues from the available paromomycin residue data cannot be made. Consequently, the exposure of the consumer calculated on the basis of total residues of toxicological concern according to Regulation (EC) No 429/2008 cannot be established.

However, considering that paromomycin sulphate appears not to be metabolised to a significant extent, it is likely that the parent compound represents most of the residues in tissues. Accordingly, a ratio of 0.8 has been retained as the worst case scenario. Consequently, the exposure of the consumer has been calculated based on the paromomycin sulphate residue levels in the different tissues (see Section 3.2.1.2.) after a ten-day withdrawal and theoretical consumption figures (Regulation (EC) No 429/2008). As the residues in liver, kidney and muscle were all below the LOQs of the analytical method (0.6, 0.6 and 0.2 mg kg^{-1} tissue, respectively) these LOQs have been retained for calculation, representing a conservative approach. A residue of 0.5 mg kg^{-1} has been retained for skin/fat, taken from the limited data from the study in chickens (value after seven days of withdrawal instead of ten, but with a lower dosage, 280 instead of 400 mg paromomycin sulphate kg^{-1} feed). Under those conditions, the consumer exposure would be 0.214 mg day^{-1}, which represents about 10 % of the toxicological ADI. This margin of safety would compensate for the uncertainties concerning the residue levels in skin/fat.

3.2.3.3. MRLs

The setting of an MRL is based on the ratio marker residue vs. total residues at the proposed withdrawal time and the availability of a suitable sensitive analytical method.

As a conservative approach, a ratio of 0.8 has been retained.

The analytical method used to measure paromomycin sulphate in turkey tissues has been validated, with LOQs of 0.2, 0.6 and 0.6 mg kg^{-1} for muscle, liver and kidney, respectively. As no LOQ was established/available for skin/fat, it was assumed it would be identical to that for liver and kidney, i.e. 0.6 mg kg^{-1}. According to Regulation (EC) No 429/2008, MRLs should be preferably not less than three times the LOQs, i.e. 0.6, 1.8, 1.8 and 1.8 mg kg^{-1}, respectively.

MRLs have been proposed by EMEA/CVMP (2002) based on the LOQs of the analytical method available for the determination of paromomycin sulphate residues in tissues of other animal species, i.e. 0.25, 0.75 and 0.75 mg kg^{-1} for muscle, liver and kidney, respectively. Twice those values were retained as MRLs, considering that paromomycin sulphate constituted the whole residues in tissues. The corresponding theoretical exposure of the consumer represented 21 % of the microbiological ADI.

It can be concluded that the MRLs proposed for turkeys for fattening are not essentially different from those already proposed by EMEA/CVMP for poultry and the other species (1.5 mg kg^{-1} for liver and kidney, 0.5 mg kg^{-1} for muscle). Taking into account different uncertainties related to the data available for turkeys, the FEEDAP Panel applied worst case scenarios. Consequently, with the intent to harmonise the approach, it proposes to adopt the MRLs already established for muscle, liver and kidney. Moreover, considering the very limited data available for skin/fat, the FEEDAP Panel proposes to set an additional provisional MRL of 1.5 mg kg^{-1} for that tissue. The set of MRLs proposed by the FEEDAP Panel for turkey tissues would then be 1.5 mg kg^{-1} for liver and kidney, 0.5 mg kg^{-1} for muscle and 1.5 mg kg^{-1} for skin/fat. The corresponding consumer exposure would represent about 28 % of the toxicological ADI or about 38 % of the microbiological ADI set by EMEA/CVMP (Table 3).

Table 3. **Safety of the proposed MRLs for paromomycin sulphate in turkey**

	Liver	Kidney	Muscle	Skin/fat	Sum
Ratio marker/total residues	0.8	0.8	0.8	0.8	
Proposal for MRL (mg kg^{-1})	1.5	1.5	0.5	1.5	
Consumption (kg day^{-1})	0.1	0.01	0.3	0.09	
Daily intake of total residues (mg kg^{-1})	0.188	0.019	0.188	0.169	0.564
Consumption (% toxicological ADI)	9	1	9	9	28

3.2.3.4. Proposal for a withdrawal time

In line with the consumer safety assessment, a withdrawal time of ten days is proposed for turkeys for fattening.

3.3. Safety for the user

According to the applicant, histoBloc® is harmful by inhalation and if swallowed. It is also irritating to the eyes. Other issues, such as the potential for sensitisation, have not been considered.

3.4. Safety for the environment

The active ingredient is not a physiological/natural substance of established safety for the environment. The additive is not intended either for companion animals. Consequently, according to Regulation (EC) No 429/2008, the Phase I assessment has to be continued to determine the predicted environmental concentration.

In Phase I and II, initially a total residues approach will be taken, meaning that the PECs will be calculated, based on the assumption that the additive is excreted at 100 % as parent compound.

The PEC_{soil} has been calculated according to the technical guidance for assessing the safety of feed additives for the environment (EFSA, 2008). The $PEC_{groundwater}$ has been preliminary estimated using the QSAR calculations for adsorption because of the absence of experimental data. The PECs are 1.8 mg kg^{-1} for soil and 6.2 mg L^{-1} for groundwater. The Phase I PEC trigger value for soil (10 μg kg^{-1}) and groundwater (0.1 μg L^{-1}) are considerably exceeded.

The FEEDAP Panel notes that a Phase II assessment is necessary. In the absence of any data on the fate and ecotoxicity of paromomycin sulphate, the FEEDAP Panel cannot conclude on the safety of histoBloc® for the environment.

4. Efficacy

4.1. Cage studies

The applicant submitted two cage studies in two different locations carried out with histoBloc® and artificial inoculation with *Histomonas meleagridis*.

The first study[9] was carried out with 100 one-day-old female turkeys divided into four treatment groups of 20 birds in five isolators, two isolators for the infected untreated group and one for the other experimental groups. The animals were fed for 34 days an unsupplemented basal diet and diets supplemented with 100, 200 or 400 mg paromomycin sulphate kg^{-1} (analytically confirmed). On day 19 of the trial, 15 turkeys per treatment group were inoculated intracloacally two times with 150 000 histomonads of *Histomonas meleagridis* (strain not defined). Mortality was checked daily and all dead animals were necropsied; on day 15 post-infection, all the remaining birds were euthanised and necropsied. All birds were checked for typical histomoniasis lesions in caecum and liver.

The results of the trial showed that paromomycin sulphate from histoBloc® decreased significantly the mortality and lesion scores of caecum and liver at the lowest (100 mg kg^{-1} feed) and the highest recommended dose (400 mg kg^{-1} feed) but not at the intermediate dose (Table 4).

[9] Technical Dossier/Section IV/Reference 4

The second study[10] was carried out with 130 one-day-old BUT BIG 6 male turkeys divided into five treatment groups, one of ten birds in the uninfected untreated group and 30 birds in three replicates in the four other groups. The animals were fed for 42 days an unsupplemented basal diet and diets supplemented with 100, 200 or 400 mg paromomycin sulphate kg^{-1} (analytically confirmed). On day 21 of the trial, the turkeys of the infected groups were inoculated intracloacally with 150 000 histomonads of *Histomonas meleagridis* (strain Turkey/ Germany/GB 551/04). Mortality was checked daily and all dead animals were necropsied; on day 21 post-infection, all the remaining birds were euthanised, necropsied and checked for typical histomoniasis lesions in caecum and liver.

The results of the trial showed that paromomycin sulphate from histoBloc® decreased mortality rate and lesion scores of caecum and liver at the dose levels of 200 and 400 mg kg^{-1} feed (Table 4).

Table 4. **Results obtained in cage trials with artificial *Histomonas* infection**

Trial	Treatment	Feed[(a)]	Mortality (%)	Caecum lesion score	Liver lesion score
1	Infected	Untreated	80[a]	3.40[ab]	3.40[a]
	Infected	histoBloc® (100 mg kg^{-1})	33[b]	2.53[bc]	2.53[ab]
	Infected	histoBloc® (200 mg kg^{-1})	73[a]	3.60[a]	3.60[a]
	Infected	histoBloc® (400 mg kg^{-1})	13[b]	1.73[c]	1.73[b]
2	Uninfected	Untreated	0	0.00	0.00
	Infected	Untreated	80	3.20	3.20
	Infected	histoBloc® (100 mg kg^{-1})	73	2.80	2.93
	Infected	histoBloc® (200 mg kg^{-1})	43	1.70	1.73
	Infected	histoBloc® (400 mg kg^{-1})	20	0.80	0.80

[(a)] concentrations are given in mg paromomycin sulphate
[a,b] different superscripts in the same column in a given trial indicate significant differences ($p < 0.05$)

4.1.1. Literature finding

Hu and McDougald published in 2004 a study in which the *in vitro* an *in vivo* (in chickens) efficacy of several drugs against *Histomonas meleagridis* has been compared. While nitroimidazoles (e.g. dimetridazole, formerly authorised as histomonostat in the EU) suppressed the growth of *Histomonas meleagridis in vitro* at 10 µg mL^{-1} or higher, paromomycin sulphate was weakly effective at high levels (10 and 100 µg mL^{-1}). In a chicken model, the nitroimidazoles were highly effective at 200 mg kg^{-1} feed, whereas paromomycin sulphate was ineffective (at 200 and 400 mg kg^{-1} feed), with no improvement in liver or caecal lesion scores.

4.2. Controlled floor pen studies

The applicant submitted four floor pen studies simulating field conditions in two different locations carried out with histoBloc® and artificial inoculation with *Histomonas meleagridis*.

The first study[11] was carried out with 100 one-day-old turkeys (sex ratio: 1:1) divided into five treatment groups of 20 birds in one pen per treatment. The animals were fed for 42 days an unsupplemented basal diet and diets supplemented with 100, 200 or 400 mg paromomycin sulphate kg^{-1}(analytically confirmed). On day 14 of the trial, ten (five females and five males) turkeys of the infected groups were inoculated intracloacally with 200 000 histomonads of

[10] Technical Dossier/Section IV/Reference 6
[11] Technical Dossier/Section IV/Reference 1

Histomonas meleagridis (strain Deventer/ NL/AL327-type I) and served as seeder birds. Mortality was checked daily and all dead animals were necropsied; on day 16 post-infection all the remaining seeder birds and on day 28 post-infection all the remaining contact birds were euthanised, necropsied and checked for histomoniasis lesions in caecum and liver. However, numerical data of the lesion scores of caecum and liver were not given. The body weight of the remaining turkeys was measured weekly.

The results of the trial showed that 400 mg paromomycin sulphate kg^{-1} reduced mortality and restored body weight to the level observed in the uninfected untreated group (Table 5).

Table 5. **Mortality of turkeys with artificial *Histomonas* infection**

Trial	Treatment	Feed[(a)]	Mortality[(b)] (%)	
			Female	Male
1	Uninfected	Untreated	0.0	9.1*
	Infected	Untreated	100.0	80.0
	Infected	histoBloc® (100 mg kg^{-1})	100.0	90.0
	Infected	histoBloc® (200 mg kg^{-1})	18.2	100.0
	Infected	histoBloc® (400 mg kg^{-1})	0.0	0.0

[(a)] Concentrations are given in mg paromomycin sulphate
[(b)] Overall mortality and culling (*) during the 30-days period post-infection

The second trial[12] was carried out with 300 one-day-old BUT BIG 6 male turkeys divided into five treatment groups of 60 birds (three replicates with 20 birds each per treatment). The animals were fed for 49 days an unsupplemented basal diet and diets supplemented with 100, 200 or 400 mg paromomycin sulphate kg^{-1} (analytically confirmed). On day 19 of the trial, ten turkeys per replicate of the infected groups were inoculated intracloacally twice with 100 000 histomonads of *Histomonas meleagridis* (strain PCH.C1.A.L3) and served as seeder birds. Mortality was checked daily and all dead animals were necropsied; on day 16 post-infection, the remaining seeder birds and on day 30 post-infection the remaining contact birds were euthanised and necropsied. All birds were checked for histomoniasis lesions in caecum and liver.

The results of the trial showed that paromomycin sulphate from histoBloc® reduced significantly the mortality and lesion scores of caecum and liver at all dose levels (Table 6); however, the effect was not dose-dependent.

The third trial[13] was carried out with 400 one-day-old BUT BIG 6 male turkeys divided into five treatment groups of 80 birds (four replicates of 20 birds each per treatment). The animals were fed for 49 days an unsupplemented basal diet and diets supplemented with 100, 200 or 400 mg paromomycin sulphate kg^{-1} (analytically confirmed). On day 16 of the trial, ten turkeys per replicate of the infected groups were inoculated intracloacally twice with 350 000 histomonads of *Histomonas meleagridis* (strain HNA.C2B.L2) and served as seeder birds. Mortality was checked daily and all dead animals were necropsied; on day 11 post-infection, the remaining seeder birds and on day 33 post-infection all the remaining contact birds were euthanised and necropsied. All birds were checked for histomoniasis lesions in caecum and liver.

The results of the trial showed that paromomycin sulphate from histoBloc® decreased significantly mortality and lesion scores of caecum and liver dose-dependently (Table 6).

[12] Technical Dossier/Section IV/Reference 2
[13] Technical Dossier/Section IV/Reference 3

The fourth trial[14] was carried out with 160 one-day-old BUT BIG 6 male turkeys divided into five treatment groups of 32 birds (four replicates of eitght birds each per treatment). The animals were fed for 49 days an unsupplemented basal diet and diets supplemented with 100, 200 or 400 mg paromomycin sulphate kg^{-1} (analytically confirmed). On day 21 of the trial, four turkeys per replicate of the infected groups were inoculated intracloacally with 100 000 histomonads of *Histomonas meleagridis* (strain not defined) and served as seeder birds. Mortality was checked daily and all dead animals were necropsied; on day 28 post-infection, all the remaining birds were euthanised and necropsied. All birds were checked for histomonosis lesions in caecum and liver.

The results of the trial showed that paromomycin sulphate from histoBloc® decreased significantly mortality and lesion scores of caecum and liver at all dose levels (Table 6).

Table 6. **Results obtained in cage trials with artificial *Histomonas* infection**

			Mortality (%)		Caecum lesion score		Liver lesion score	
Trial	**Treatment**	**Feed[(a)]**	**Seeder**	**Contact**	**Seeder**	**Contact**	**Seeder**	**Contact**
	Uninfected	Untreated	0.0	0	0.77	0	0	0
	Infected	Untreated	70.0[a]	0	3.00[a]	0	3.00[a]	0
2	Infected	histoBloc® (100 mg kg^{-1})	33.3[b]	0	1.33[b]	0	1.43[b]	0
	Infected	histoBloc® (200 mg kg^{-1})	46.7[b]	0	2.27[b]	0	1.97[b]	0
	Infected	histoBloc® (400 mg kg^{-1})	30.0[b]	0	1.86[b]	0	1.34[b]	0
	Uninfected	Untreated	0	0	0.43	0	0	0
	Infected	Untreated	97.5[a]	2.5	3.98a	0	3.98a	0
3	Infected	histoBloc® (100 mg kg^{-1})	70.0[b]	0	3.33[b]	0	3.18[b]	0
	Infected	histoBloc® (200 mg kg^{-1})	50.0[b]	0	2.75[b]	0	2.53[b]	0
	Infected	histoBloc® (400 mg kg^{-1})	10.0[b]	0	1.05[b]	0	0.40[b]	0
	Uninfected	Untreated	0	0	0	0	0	0
	Infected	Untreated	75.0[a]	0	3.00a	0	3.00a	0
4	Infected	histoBloc® (100 mg kg^{-1})	56.3[b]	0	2.25[b]	0	2.25[b]	0
	Infected	histoBloc® (200 mg kg^{-1})	31.3[b]	0	1.25[b]	0	1.25[b]	0
	Infected	histoBloc® (400 mg kg^{-1})	50.0[b]	0	2.00[b]	0	2.00[b]	0

[(a)] Doses are given as the amount of paromomycin sulphate
[a,b] Different superscripts in the same column indicate significant differences as compared to infected untreated group ($p < 0.05$)

In all those trials, the contact birds showed no signs of infection.

4.3. Field trials

The applicant provided three sets of field trials carried out under field conditions in three different countries.[15,16,17] A total of 175 000 turkeys for fattening/reared for breeding received diets supplemented with histoBloc® (100 mg paromomycin sulphate kg^{-1} feed, for 17 weeks in two sets, for eight weeks in the other set) and another 101 600 turkeys received an unsupplemented control diet. The different treatment groups were allocated to different houses or farms. Clinical evidence of histomoniasis in the untreated flocks could not be observed in any of the experimental locations. Histomonads could not be found in faeces or dust emitted by the turkey operations. In all three trials, similar zootechnical performance and mortality were observed in the treated and control flocks. An assessment of the

[14] Technical Dossier/Section IV/Reference 5
[15] Technical Dossier/Section IV/Reference 12
[16] Technical Dossier/Section IV/References 13 and 14
[17] Technical Dossier/Section IV/Reference 15

histomonostatic efficacy of histoBloc® in turkeys under field conditions is therefore not possible.

4.4. Quality of the animal product

No data on the possible effect of paromomycin on the quality of animal products was provided.

4.5. Conclusions on the efficacy for target species

Two battery cage and four floor pen studies with artificial infection support the efficacy of paromomycin sulphate from histoBloc® in turkeys for fattening. Taking all six trials together, mortality decreased dose-dependently (82, 60, 51 and 21 % for 0, 100, 200 and 400 mg paromomycin sulphate kg^{-1}, respectively). Paromomycin sulphate at 100 mg kg^{-1} feed is of limited efficacy, the highest reduction of mortality and intestinal lesion scores was observed with 400 mg paromomycin kg^{-1}, the highest dose tested. However, none of the pen trials was conducted according to the minimum duration required.

In the absence of evidence of histomoniasis, none of the field trials (involving 27 farms) is relevant to the demonstration of the efficacy of paromomycin as histomonostat. The zootechnical performance and mortality were not different in the treated and control flocks.

Due to the complete lack of data under practical conditions and despite the likely efficacy of paromomycin sulphate against histomoniasis in turkeys, a conclusion on the efficacy of histoBloc® under field conditions, particularly on the effective dose, is not possible.

No data were available to assess the influence of histoBloc® on the quality of animal products.

5. Post-market monitoring

Since paromomycin sulphate has been experimentally demonstrated to select for bacterial cross-resistance against other antibiotics, particularly aminoglycosides, the development of bacterial cross-resistance under field conditions should be monitored, beginning immediately after a potential authorisation of paromomycin sulphate as feed additive.

Field monitoring of *Histomonas meleagridis* resistance to the histomonostat should be undertaken, preferably during the latter part of the period of authorisation.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

The safety of paromomycin sulphate from histoBloc® in turkeys when fed continuously for 16 weeks at the highest proposed dose (400 mg kg^{-1} diet) could not be established due to the absence of data.

Paromomycin sulphate shows an antimicrobial effect on susceptible bacterial strains at levels considerably lower than those proposed for feed use. Paromomycin sulphate, even at the lowest proposed feed concentration (100 mg kg^{-1} diet), selects for resistance and cross-resistances at high frequency against a variety of other aminoglycosides among intestinal bacteria. As aminoglycoside antibiotics are used in human and veterinary medicine, serious consequences on the antibiotic therapy in humans and animals can be anticipated.

The limited data available on paromomycin sulphate metabolism indicate that (i) orally administered paromomycin sulphate is absorbed to a very limited extent, (ii) negligible biotransformation occurs following absorption, (iii) no accumulation in tissues occurs (with the exception of the kidney) and (iv) paromomycin sulphate constitutes most of the residues in tissues. Paromomycin sulphate is the marker residue. No conclusions on the similarity of the metabolic fate of paromomycin in sulphate turkeys and laboratory animals can be drawn.

Paromomycin sulphate has a very low oral acute toxicity, it is not mutagenic, genotoxic, carcinogenic or teratogenic. Oral chronic toxicity in dogs resulted in the lowest NOEL of approximately 3.4 mg paromomycin sulphate kg^{-1} bw.

A residue study with histoBloc® in turkeys, at the highest dose proposed for use (400 mg kg^{-1} feed) indicates that the highest concentrations occur in kidney, followed by muscle and liver. No measurement was performed in skin/fat. The FEEDAP Panel estimates consumer exposure after a ten-day withdrawal, extrapolating skin/fat data from a chicken study, to 0.214 mg day^{-1}, representing about 10 % of the toxicological ADI.

As MRLs, the FEEDAP Panel retains the EMEA/CVMP values for liver, kidney and muscle (1.5, 1.5 and 0.5 mg kg^{-1}, respectively) and adds a provisional value of 1.5 mg kg^{-1} for skin/fat. The corresponding consumer exposure would represent 28 % of the toxicological ADI. A withdrawal time of ten days is proposed for turkeys for fattening.

According to the applicant, histoBloc® is harmful by inhalation and if swallowed. It is also irritating to the eyes. Other issues, such as the potential for sensitisation, have not been considered.

Preliminary calculations indicate that the trigger values for soil and groundwater would be exceeded and thus a Phase II assessment is needed. In the absence of any experimental data on the fate and ecotoxicity of paromomycin sulphate, the FEEDAP Panel cannot conclude on the safety of histoBloc® for the environment.

From battery cage and floor pen studies, a dose-dependent effect of histoBloc® on mortality due to histomoniasis could be derived (82, 60, 51 and 21 % for 0, 100, 200 and 400 mg paromomycin sulphate kg^{-1}, respectively). Paromomycin sulphate at 100 mg kg^{-1} feed is of limited efficacy, the highest reduction of mortality and intestinal lesion scores was observed with 400 mg paromomycin sulphate kg^{-1}, the highest dose tested. Field trials could not demonstrate the efficacy of paromomycin sulphate due to the absence of histomoniasis. A conclusion on the efficacy of histoBloc® under field conditions, particularly on the effective dose, is therefore not possible.

No data were available to assess the influence of histoBloc® on the quality of animal products.

RECOMMENDATIONS

Protective measures and restrictions in handling histoBloc® should be considered.

A post-market monitoring plan should be implemented immediately after any authorisation.

A potential authorisation of the product should describe the composition of histoBloc® as 80 g paromomycin sulphate kg^{-1} additive, calcium carbonate and pre-gelatinised starch.

A validated analytical method for the determination of paromomycin sulphate in skin/fat should be developed.

DOCUMENTATION PROVIDED TO EFSA

1. histoBloc® (paromomycin) dossier. January 2009. Submitted by Huvepharma NV.
2. Comments from Member States received through the ScienceNet.

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