European Medicines Agency
Veterinary Medicines and Inspections

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

LASALOCID
(Extension to eggs)

SUMMARY REPORT

1. Lasalocid is an antibiotic from the group of carboxylic ionophores. Lasalocid is used as the sodium salt (CAS No 25999-20-6). Lasalocid is produced by *Streptomyces lasaliensis* and is a mixture of several closely related homologue substances A, B, C, D, and E. The sum of the lasalocid homologues B, C, D, and E is limited to 10% of the total weight of the active substance, lasalocid. The substance is mainly active against Gram positive microorganisms. In veterinary medicine lasalocid is used in birds for the prevention of coccidiosis caused by *Eimeria spp at* doses of 75 to 120 mg/kg in feed for fattening chickens, 90 to 120 mg/kg in feed for turkeys and 90 to 120 mg/kg in feed for pheasants, partridges and quails. In laying birds the recommended doses are 75 to 125 mg/kg in feed for hens, 90 to 120 mg/kg for game birds (e.g, pheasants, partridges) and 90 to 125 mg/kg for turkeys.

   Lasalocid is authorised as a feed additive under Council Directive 70/524/EEC for the prevention of coccidiosis in chickens and turkeys. As a feed additive the substance is given continuously to chickens from day 0 up to 16 weeks, at doses of 75 to 125 mg/kg in feed with a withdrawal period of 5 days and to turkeys at doses of 90 to 125 mg/kg up to a maximum age of 12 weeks and with a withdrawal period of 5 days.

   Lasalocid is not used in human medicine.

   Currently, lasalocid is included in Annex I of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissue	Other provisions
Lasalocid	Lasalocid A	Poultry	20 µg/kg 100 µg/kg 100 µg/kg 50 µg/kg	Muscle Skin + fat Liver Kidney	

   and in Annex III as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissue	Other provisions
Lasalocid	Lasalocid A	Poultry	150 µg/kg	Eggs	Provisional MRLs expire on 1 January 2008

[1] The dose for laying hens under point 3 has been corrected from µg to mg.

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2. The information requested for the establishment of a final MRL for lasalocid in poultry eggs has now been provided. The CVMP, having evaluated the response to the List of Questions, has considered that the provisional MRL can be confirmed as final. A summary of the assessment is provided below.

3. Radiolabelled lasalocid sodium was orally administered to 24 broiler laying hens for 12 consecutive days. The product was administered daily, divided into three doses in order to simulate administration of medicated feed at a concentration of 125 mg/kg of lasalocid. The eggs were collected during treatment (12 days) and after treatment for 21 days. The animals were divided into two groups of 12 animals; the first group was used to quantify the radioactive residues in albumin and egg yolk separately and the second one to study the lasalocid residues in whole egg. The total radioactive residues were quantified with a liquid scintillation analyser. The peak total radioactive residue concentrations (291 µg/kg) found in albumin were lower than those found in egg yolk (32500 µg/kg) indicating a great affinity of the lasalocid residues for egg yolk. The concentrations of total radioactive residues in egg yolk increased during treatment until day 7 indicating that in this tissue, steady state residue concentrations are very difficult to achieve. However, in albumin, steady state is achieved after 3 days of treatment. Whole egg total radioactive residues follow a concentration pattern similar to egg yolk, but at lower concentrations with mean steady state concentrations of about 11000 to 12000 µg/kg. After the end of treatment the total radioactive residue concentrations decline slowly over ten days (207 µg/kg), indicating that lasalocid residues remain in the egg for a long time. Whole egg samples corresponding to 0, 8, 9, and 10 days after treatment were analysed by HPLC to quantify lasalocid A concentrations in order to calculate the marker to total residue ratio. The resulting ratios were between 0.5 at the end of treatment and 0.26 ten days after discontinuing treatment. The marker residue concentrations 0, 8, 9 and 10 days after treatment were 6206, 460, 128 and 61 µg/kg respectively. Lasalocid A was retained as the marker residue in eggs and represents 37.5% of the total residues in eggs at 9 days after treatment.

   The chromatographic separation of the whole egg residue extracts showed mean peak area percentages of lasalocid A of 59.5, 64.4 and 65.8 at 2, 8 and 9 days after treatment. The main metabolite observed represents 27 to 29% of the total radioactive area and the other metabolites represent 2 to 4% only. The molecular structure of the metabolites was elucidated by LC/MS/MS, and the results show that the radiolabelled metabolites present in the whole egg were a result of oxidation and/or hydroxylation of the lasalocid A molecule.

4. A routine LC-MS/MS method to determine the marker residue (lasalocid A) in whole egg is available according to ISO 78/2 standard format. The method is applicable in the range of 10 to 750 µg/kg with a limit of quantification (LOQ) of 10 µg/kg and limit of detection (LOD) of 0.093 µg/kg. Accuracy and precision were satisfactorily addressed. Specificity was demonstrated in the presence of the other ionophore substances maduramycin, salinomycin, narasin, monensin, semduramycin, nicarbazin and robenidine. The stability of lasalocid A in the matrix at storage conditions was also proved. The method was validated according to Volume 8 of the Rules Governing Medicinal Products in the European Union.

Conclusion and recommendations

Having considered that:

- an ADI of 2.5 µg/kg/day (i.e. 150 µg/ 60 kg bw person/day) has been established based on the toxicological studies,
- lasalocid A was identified as marker residue in eggs and represents 37.5% of the total residues in eggs at 9 days after treatment,
- a validated analytical method is available for monitoring of residues of lasalocid in eggs;

the Committee for Medicinal Products for Veterinary Use recommends the modification of the entry for lasalocid in Annex I of Council Regulation (EEC) No 2377/90 to include eggs, in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Lasalocid	Lasalocid A	Poultry	20 µg/kg 100 µg/kg 100 µg/kg 50 µg/kg 150 µg/kg	Muscle Skin + fat Liver Kidney Eggs	

Based on the MRL value for eggs and the established MRL values for tissues, the theoretical daily intake represents about 78.4% of the ADI.