The European Agency for the Evaluation of Medicinal Products

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

FLUBENDAZOLE (extension to turkeys)

SUMMARY REPORT

1. Flubendazole is a benzimidazole anthelmintic which is administered orally to pigs, chickens and game birds.

   An ADI of 12 µg/kg bw, i.e. 720 µg/person was previously established by the Committee on Veterinary Medicinal Products (CVMP).

   Flubendazole is currently entered into Annex I of Council Regulation (EEC) No. 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Flubendazole	Sum of flubendazole and (2-amino-1*H*-benzimidazole-5-yl) (4-fluorophenyl)-methanone	Porcine, chicken, game birds	50 µg/kg 50 µg/kg 400 µg/kg 300 µg/kg	Muscle Skin + fat Liver Kidney	
	Flubendazole	Chicken	400 µg/kg	Eggs	

   An application has now been submitted for the extension of the MRLs for flubendazole to turkeys. The substance is administered at a concentration of 20 mg/kg in the feed for up to 7 days, equivalent to 0.56 to 2.35 mg/kg bw/day, depending on the age of the bird.

2. Data on the pharmacokinetics and metabolism of flubendazole were provided for laying hens. Following oral administration of ^{14}C-flubendazole at a dose equivalent to 60 mg/kg feed for 7 consecutive days, absorption was rapid. A C_{max} value of 0.24 µg equivalents/ml was obtained 4 hours after the initial dose. A slightly higher C_{max} value of 0.28 µg equivalents/ml was obtained approximately 5 hours after the 7th dose. There was no evidence of bioaccumulation with around 90% of the administered dose eliminated in excreta each day. Twenty-four hours after the last dose, approximately 60% of the residues in omental fat and 35% of the residues in skin + fat consisted of unmetabolised flubendazole. However, flubendazole accounted for less than 3% of the total residues in liver and kidney and these organs contained residues of the metabolites (2-amino-1*H*-benzimidazole-5-yl)(4-fluorophenyl)methanone (7.9% and 5.8% of the residues in liver and kidney) and methyl[5-(fluorophenyl)hydroxymethyl]-1*H*-benzimidazole-2-yl]carbamate (5.3% and 1.4% of the residues in liver and kidney). An *in vitro* metabolism study using chicken and turkey hepatocytes confirmed that ketoreduction to methyl[5-(fluorophenyl)hydroxymethyl]-1*H*-benzimidazol-2-yl]carbamate was the major metabolic pathway in both species.

3. The sum of flubendazole and (2-amino-1*H*-benzimidazole-5-yl)(4-fluorophenyl)-methanone was previously identified as the marker residue for chicken tissues; taking into account the CVMP Note for Guidance on the establishment of MRLs for minor animal species (document

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EMEA/CVMP/153a/97), it was considered that the same marker residue and MRL values were appropriate for the edible tissues of turkeys.

4. Turkeys were fed diets containing flubendazole at 30 mg/kg feed for 7 days. Three male birds and three female birds were killed at 6 hours, one day, 3 days, 5 days, 7 days and 9 days after the end of treatment. Residues of flubendazole and its metabolites in tissues were determined using HPLC. The limits of quantification were: for flubendazole: 10 µg/kg for all tissues; for (2-amino-1*H*-benzimidazole-5-yl)(4-fluorophenyl)methanone and methyl[5-(fluorophenyl)hydroxymethyl]-1*H*-benzimidazol-2-yl]carbamate: 25 µg/kg for liver and 10 µg/kg for other tissues; and for 2-amino-alpha-(4-fluorophenyl)-1*H*-benzimidazole-5-methanol: 50 µg/kg for skin + fat and 10 µg/kg for other tissues. Six hours after the end of treatment mean residues of flubendazole in liver, kidney, muscle and skin + fat were 64, 67, 18 and 60 µg/kg respectively. Six hours after the end of treatment, mean residues of methyl[5-(fluorophenyl)hydroxymethyl]-1*H*-benzimidazol-2-yl]carbamate in these tissues were 200, 80, 42 and 32 µg/kg respectively. At the same time point, low residues of (2-amino-1*H*-benzimidazole-5-yl) (4-fluorophenyl)methanone were found in liver (29 µg/kg) and kidney (11 µg/kg) but not in muscle or skin + fat. At six hours low residues of 2-amino-alpha-(4-fluorophenyl)-1*H*-benzimidazole-5-methanol were found in kidney (10 µg/kg) and in liver but an interfering peak prevented the quantification of the residues in liver; residues of (2-amino-a-(4-fluorophenyl)-1*H*-benzimidazole-5-methanol were undetectable in muscle and skin + fat. One day after the end of treatment, detectable residues of flubendazole were found only in a sample of skin + fat from one bird (11 µg/kg) and detectable residues of methyl[5-(fluorophenyl) hydroxymethyl]-1*H*-benzimidazol-2-yl]carbamate were found only in the kidney of one bird (18 µg/kg); residues in other tissues and residues at all later time-points were below the respective limits of quantification.

5. A validated analytical method for the determination of residues of flubendazole and the metabolite (2-amino-1*H*-benzimidazole-5-yl)(4-fluorophenyl)-methanone in the edible tissues of turkeys was provided. The method was the same as that which had previously been developed for the edible tissues of chickens and was based on HPLC with UV detection. The limits of quantification for each analyte were 100 µg/kg for turkey liver, 75 µg/kg for turkey kidney and 10 µg/kg for turkey muscle and skin + fat. A description of the method in the ISO 78/2 format was provided.

Conclusions and recommendation

Having considered that:

- an ADI of 12 µg/kg bw, i.e. 720 µg/person, was previously established for flubendazole,
- the sum of flubendazole and (2-amino-1*H*-benzimidazole-5-yl)(4-fluorophenyl)-methanone was the appropriate marker residue for turkeys,
- an analytical method based on HPLC, which had been validated for the edible tissues of turkeys was available;

the Committee for Veterinary Medicinal Products recommends the inclusion of flubendazole 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 tissues	Other provisions
Flubendazole	Sum of flubendazole and (2-amino-1*H*-benzimidazole-5-yl)(4-fluorophenyl)-methanone	Turkeys	50 µg/kg 50 µg/kg 400 µg/kg 300 µg/kg	Muscle Skin + fat Liver Kidney	

Based on the above MRLs, the daily intake of total residues from meat and eggs will represent approximately 80% of the ADI.