The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Information Technology Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DICYCLANIL
(Modification of the MRL for fat)

SUMMARY REPORT (3)

1. Dicyclanil is a pyrimidine-derived insect growth regulator which is used in veterinary medicine for the prevention of myiasis or fly-strike. The target species is sheep with a recommendation for one application per season at a therapeutic dose of 30 to 100 mg/kg bw. The compound is applied topically in a suspoemulsion pour-on formulation, with a dicyclanil concentration of 50 mg/ml.

   An ADI of 7 µg/kg bw, i.e. 0.42 mg per person, had been previously established by the Committee for Veterinary Medicinal Products.

   Currently, dicyclanil is included in Annex III of Council Regulation No 2377/90 in accordance with the following table:

Pharmacologically active substances(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Dicyclanil	Sum of dicyclanil and 2,4,6-triamino-pyrimidine-5-carbonitrile	Ovine	200 µg/kg 50 µg/kg 400 µg/kg 400 µg/kg	Muscle Fat Liver Kidney	Provisional MRLs expire on 1.7.2000 Not for use in animals from which milk is produced for human consumption.

   Recently the CVMP recommended the inclusion of dicyclanil in Annex I with the same MRL values and the same provisions as stated above.

   An application has now been submitted for a modification of the MRL for fat tissue. The application involves increasing the MRL for fat from the current value of 50 µg/kg to a higher value of 150 µg/kg.

2. A GLP compliant residue depletion study was conducted in White Alp sheep treated with a pour-on formulation of dicyclanil at a dose rate of 100 mg/kg bw. Treated animals were shorn 1 day or 7 weeks prior to application of dicyclanil. Groups of 6 animals per fleece length were slaughtered at 7, 14, 21 or 35 days post treatment. Dicyclanil and its metabolite 2,4,6-triamino-pyrimidine-5-carbonitrile were assayed by HPLC, with an limit of quantification of the analytical technique of 10 µg/kg. The metabolite 2,4,6-triamino-pyrimidine-5-carbonitrile was the dominant residue fraction in liver and kidney, whilst parent compound predominated in fat. In muscle, both parent compound and 2,4,6-triamino-pyrimidine-5-carbonitrile were present in similar amounts. The mean residue concentrations recorded in liver were 130 µg/kg and 250 µg/kg for dicyclanil and 2,4,6-triamino-pyrimidine-5-carbonitrile respectively, at the 7 day time point.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 47
E-mail: mail@emea.eudra.org http://www.eudra.org/emea.html
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These values declined to 30 and 70 µg/kg for parent compound and metabolite respectively, at the 21 day time point. In the case of kidney, mean residue concentrations of 80 and 180 µg/kg for dicyclanil and 2,4,6-triamino-pyrimidine-5-carbonitrile were detected at the 7 day time point. The corresponding values at day 21 were 20 and 60 µg/kg for parent compound and metabolite respectively. Residues of dicyclanil in fat varied significantly with the site of sampling. The highest mean concentrations of residues were detected in omental fat and subcutaneous fat, distal to the site of application. The highest mean residue concentration detected was 390 µg/kg of parent compound in omental fat at the 7 day time point. The corresponding value was 130 µg/kg at the 21 day time point.

Mean residue concentrations in renal fat and subcutaneous fat at the site of application were of a significantly lower magnitude. Although 3 different muscle sites were sampled, there were no significant differences in the mean residue concentrations detected between the sites. Highest mean residue concentrations of 90 µg/kg and 70 µg/kg of parent compound and 2,4,6-triamino-pyrimidine-5-carbonitrile respectively, were detected in muscle at the 7 day time point. The corresponding values at the 21 day time point were 20 and 50 µg/kg respectively.

Conclusions and recommendation

Having considered that:

- an ADI of 0.42 mg/person was established,
- the sum of dicyclanil and metabolite 2, 4, 6-triamino-pyrimidine-5-carbonitrile was identified as marker residue and considering that the marker residue represents approximately 100%, 100%, 15% and 25% respectively in muscle, fat, liver and kidney at 21 days after treatment,
- further data on the depletion of residues in fat have been made available, justifying an increased MRL-value for this tissue,
- a validated analytical method for monitoring is available;

the Committee for Veterinary Medicinal Products recommends the inclusion of dicyclanil in Annex I of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substances(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Dicyclanil	Sum of dicyclanil and 2,4,6-triamino-pyrimidine-5-carbonitrile	Ovine	200 µg/kg 150 µg/kg 400 µg/kg 400 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption.

Based on these MRL values, the daily intake will represent about 98.5%of the ADI.