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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

AMITRAZ (cattle and sheep)

SUMMARY REPORT (1)

1. Amitraz is a formamidine acaricide and insecticide used on top fruit, cotton and hops, and as a veterinary medicine for the treatment of ectoparasites in pigs, cattle, sheep, goats and dogs.

2. Amitraz has been previously assessed for pigs. A final ADI of 0.003 mg/kg was established, based on a NOEL of 0.25 mg/kg bw/day from a 2-year dog study, and using a safety factor of 100. This figure was rounded in accordance with the ADI established by the JMPR (1984, 1990) based on the same toxicity data. For pig tissues final MRLs of 0.05 mg/kg for muscle, 0.2 mg/kg for liver and kidney and 0.4 mg/kg for fat and skin were established, based on the sum of amitraz and all metabolites containing the 2,4-DMA moiety, expressed as amitraz.

   Residue depletion studies, including analytical methods, have now been received for the bovine and ovine species.

3. After repeated spraying with amitraz, in calves no residues (expressed as amitraz equivalents) above 0.05 mg/kg could be detected in muscle and fat at day 1, 3, 7 and 14 after treatment. In liver and kidney only at day 1 and 3 residues could be detected (respectively 0.09 and 0.15 mg/kg at day 1, and 0.07 and 0.09 mg/kg at day 3). Residues in milk of dairy cows after repeated spraying with amitraz were highest at 7 hours after treatment (0.006-0.024 mg/l). All milk samples were below 0.01 mg/l at 48 hours after treatment, and reached 0.002 mg/l within 72-96 hours.

4. In sheep, residues (expressed as mg/kg amitraz equivalents) can be found in all tissues after dip treatment of amitraz. Highest levels were found in back fat (0.26-0.27 mg/kg at days 1, 3 and 5, and 0.12 mg/kg at day 7) and kidney (0.27 mg/kg at day 1, 0.09 and 0.07 mg/kg at days 5 and 7). Lower levels were found in omental fat (0.08-0.10 mg/kg at all time points), liver (0.13 mg/kg at day 1, and 0.04 mg/kg at days 5 and 7) and muscle (<0.05 mg/kg at all time points).

5. In line with the recently established MRLs for pig tissues and the EU MRLs for amitraz for food products of plant origin, the marker residue for amitraz for food commodities of animal origin is defined as "sum of amitraz and all metabolites containing the 2,4-DMA moiety, expressed as amitraz".

6. For the determination of amitraz in milk from cattle a GC-method with electron capture detection (based on hydrolysis of amitraz and all its derivatives containing the 2,4-DMA moiety to 2,4-DMA) is described which is poorly validated. The limit of detection (0.002 mg/kg) is not substantiated and no limit of quantification can be defined. Experimental data about most other analytical parameters are lacking.

7. For the determination of amitraz in tissues of cattle and sheep the same GC-method as for milk is described, but it is not validated according to the requirements laid down in Volume VI of the Rules Governing Medicinal Products in the European Community.

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Conclusions and recommendation

Having considered that :

- a toxicological ADI has been set at 0.003 mg/kg (180 µg/person) for amitraz;
- no validated physico-chemical analytical method is available to detect residues of amitraz in the tissues of bovine and ovine species;
- as the concentration of residues in muscle was extremely low, and was below the LOQ of the analytical method, no muscle MRL was considered necessary.

The Committee recommends the inclusion of amitraz into Annex III of Council Regulation (EEC) No 2377/90 for bovine and ovine in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Amitraz	Sum of amitraz and all metabolites containing the 2,4-DMA moiety, expressed as amitraz	Bovine	200 µg/kg	Liver, Kidney, Fat	Provisional MRLs expire on 1.7.98
			10 µg/kg	Milk	
		Ovine	400 µg/kg	Fat	
			200 µg/kg	Liver, Kidney	

Based on these MRLs, consumer intake of residues from meat would represent approximately 30% of the established ADI and, taking into account pesticide use, this ADI would not be exceeded.

LIST OF QUESTIONS

1. For the determination of amitraz in milk from cattle a GC-method with electron capture detection (based on hydrolysis of amitraz and all its derivatives containing the 2,4-DMA moiety to 2,4-DMA) is described which is poorly validated. Experimental data about the specificity, recovery, accuracy, precision, limit of detection, limit of quantitation and susceptibility to interference are insufficient or even lacking. The applicant should provide these experimental data for milk in order to fully validate this analytical method, or the GC method which is presented for the determination of residues of amitraz in pig tissues should be validated for milk from cattle. The validation should be according to the requirements laid down in Volume VI of the Rules governing medicinal products in the European Community. The method should be described in an internationally recognized standard layout (e.g. ISO 78/2).

2. The routine analytical GC method which is presented for the determination of residues of amitraz in pig tissues should be validated for tissues from cattle and sheep, according to the requirements laid down in Volume VI of the Rules governing medicinal products in the European Community. The method should be described in an internationally recognized standard layout (e.g. ISO 78/2).

3. If amitraz is also indicated for sheep delivering milk for human consumption, the applicant has to supply residue studies with lactating sheep. The applicant should then also provide a fully validated method for milk from sheep, according to the requirements laid down in Volume VI of the Rules governing medicinal products in the European Community. The method should be described in an internationally recognized standard layout (e.g. ISO 78/2).

4. From an annex to the application form it becomes clear that in some member states amitraz is also registrated for use on (lactating) goats. If the (lactating) goat is also a target animal for this MRL application, the applicant has to supply residue data on (lactating) goats in line with minor species requirements (CVMP guideline on minor species for the establishment of MRLs under Council Regulation (EEC) No 2377/90), as well as fully validated analytical method for tissues (and milk) from goats, according to the requirements laid down in Volume VI of the Rules governing medicinal products in the European Community. The methods should be described in an internationally recognized standard layout (e.g. ISO 78/2).