The European Agency for the Evaluation of Medicinal Products
*Veterinary Medicines and Inspections*

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# COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

## IMIDOCARB
## (Extension to sheep)

## SUMMARY REPORT (3)

1. Imidocarb is a carbanilide derivative with antiprotozoal activity. It is usually administered as the dipropionate salt. In veterinary medicine it is administered by subcutaneous injection to cattle (2.1 mg/kg bw) for the treatment of anaplasmosis and babesiosis.

   Imidocarb has previously been evaluated by the Committee for Veterinary Medicinal Products (CVMP). An ADI of 0.010 mg/kg bw (i.e. 0.6 mg/person) was established by applying a safety factor of 500 to the LOEL of 5 mg/kg bw/day observed in the 90-day repeated-dose toxicity study in dogs. The safety factor of 500 was applied to take into account the use of a LOEL and to compensate for the limited pathological and clinical chemistry investigations. This ADI was the same as that proposed by the Joint WHO/FAO Expert Committee on Food Additives (JECFA).

   Currently, imidocarb 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 tissues | Other provisions |
|---|---|---|---|---|---|
| Imidocarb | Imidocarb | Bovine | 300 µg/kg<br>50 µg/kg<br>2000 µg/kg<br>1500 µg/kg<br>50 µg/kg | Muscle<br>Fat<br>Liver<br>Kidney<br>Milk | |

   Imidocarb had been included before in Annex III for ovine tissues and milk with the above MRL values. At the time of that evaluation the information requested by the CVMP for ovine (relating to the proposed routine analytical method) had not been provided and therefore the establishment of final MRLs for ovine species could not be recomended.

   An application has now been submitted for the extension of the MRLs for imidocarb to sheep. Imidocarb is intended for use in sheep for the treatment of babesiosis and anaplasmosis with a recommended dose of 1.2 mg/kg bw administered by a single subcutaneous or intramuscular injection.

2. In mice dosed intravenously with $^{14}$C-imidocarb and killed 3.5 hours later, over 90% of the residues present in liver and kidney was unmetabolised imidocarb. Over 95% of the radiolabelled material in mouse urine was unmetabolised imidocarb. An *in vitro* study using bovine liver slices, isolated hepatocytes and microsomal fractions found no evidence for the metabolism of imidocarb.

3. Studies were carried out in which sheep were administered 4.5 mg imidocarb/kg bw or 50 µg/kg bw of $^{14}$C-imidocarb by intramuscular injection. The animals were killed at intervals up to 32 days after treatment (1 or 2 per time-point). The substance was widely distributed to all tissues and residues were still detectable in most tissues 32 days after treatment. There was no evidence for the formation of imidocarb metabolites in urine, bile, liver or kidney.

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4. Sheep were given two intramuscular doses of 1.2 mg/kg bw imidocarb 7 days apart. The sheep were killed (3 per time-point) 7, 14 or 28 days after the last treatment. Residues in tissues were determined using a non-specific spectrophotometric method with a claimed limit of quantification of 100 µg/kg. Residues in kidney were in the range of 22 600 to 121 200 µg/kg, 7 days after the last treatment and declined to 5600 to 9600 µg/kg, 28 days after the last treatment. Residues in liver were in the range 5700 to 14300 µg/kg, 7 days after the last treatment and declined to 900 to 3100 µg/kg, 28 days after the last treatment. In muscle, residues were in the range 1100 to 1200 µg/kg, 7 days after the last dose but only less than 100 to 400 µg/kg, 28 days after the last treatment. In fat, imidocarb concentrations ranged from less than 100 to 100 µg/kg, 7 days after the last treatment to below 100 µg/kg in all samples at days 14 and 28. Residues in injection site muscle were higher than in normal muscle but were lower than in liver and kidney; they were 700 to 2300 µg/kg, 7 days after the last treatment, less than 100 to 900 µg/kg, after 14 days and less than 100 µg/kg on day 28.

5. Sheep were treated with a single intramuscular injection in the thigh at a dose rate of 3 mg imidocarb dipropionate/kg bw. Animals were slaughtered in groups of two sheep and samples were taken at 15, 30, 60, 90 and 120 days after treatment. The samples were analysed using a spectrophotometric method with a limit of quantification of 12.5 µg/kg. Mean residues depleted in liver from 4606 µg/kg on day 15 to 1137 µg/kg on day 60 and were below the limit of quantification on day 90. Mean residues in kidney depleted from 2612 µg/kg on day 15 to 153.5 µg/kg on day 90, and values on day 120 were below the limit of quantification. Mean residues depleted from day 15 to day 30; in muscle from 28 to 26 µg/kg; in injection site from 87 to 47 µg/kg; and in subcutaneous fat from 64 to 14 µg/kg. Residues in muscle, injection site and subcutaneous fat had all depleted to below the limit of quantification by day 60. Mean residues in omental fat depleted from 74 µg/kg on day 15 to 60 µg/kg on day 60 and below the limit of quantification after day 90.

6. In a published study, 5 lactating sheep were given an intramuscular injection of imidocarb dipropionate as a dose equivalent to 4.5 mg imidocarb base/kg bw (more than 3 times the recommended dose). Samples of milk were taken from ewes at 4 and 6 hours (one ewe/time-point), 24 hours (2 ewes) and 32 days (one ewe). The samples were analysed using a spectrophotometric method with a claimed limit of detection of 1000 µg/kg. Residues of imidocarb in the milk taken from the ewes 4 and 6 hours after treatment were 4500 µg/kg and 5300 µg/kg respectively. Mean residues at 24 hours were 5600 µg/kg. Residues were undetectable in milk taken 32 days after treatment.

7. Calves and lactating dairy cows (3 in early and 3 in late lactation) were given a single subcutaneous dose of 3 mg/kg bw of $^{14}$C-imidocarb dipropionate. The animals were killed (4 or 6 per time point) at 28, 56 or 90 days after treatment. Mean total residues in liver depleted from 8240 µg equivalents/kg, 28 days after treatment, to 4010 µg equivalents/kg, 56 days after treatment and 2190 µg equivalents/kg, 90 days after treatment. Over the same time-period, mean total residues in kidney depleted from 12810 µg equivalents/kg to 3770 µg equivalents/kg to 1400 µg equivalents/kg. Mean total residues in muscle depleted from 680 µg equivalents/kg, 28 days after treatment to 410 µg equivalents/kg, 56 days after treatment and 308 µg equivalents/kg, 90 days after treatment. Over the same time-period, mean total residues in fat depleted from 130 µg equivalents/kg to 100 µg equivalents/kg to 30 µg equivalents/kg. Seventy-eight to 84% of the residues in liver, 95% of the residues in kidney and 80 to 96% of the residues in muscle were extractable. HPLC analysis indicated that 66%, 69% and 67% of the total residues in liver on days 28, 56 and 90 were imidocarb. In kidney, 82%, 92% and 91% of the residues on days 28, 56 and 90 were imidocarb. In muscle samples, 79% of the total residues on day 28, 89% on day 56 and 95% on day 90 were identified as imidocarb. At the first milking after treatment, mean residues in milk were 102 µg equivalents/kg. Peak milk residues were found at the second milking (374 µg equivalents/kg) and declined to 31 µg equivalents/kg at the 12$^{th}$ milking after treatment. Seventy seven to 95% of the milk samples were extractable. Seventy to 80% of the total residues in milk for the first 3 days after treatment consisted of imidocarb.

8. The proposed routine analytical method for ovine tissues was based on HPLC with UV detection. The method was described in the ISO 78/2 format and was fully validated at half the MRL, the MRL and twice the MRL for ovine tissues, in accordance with Volume 8 of the Rules Governing Medicinal Products in the European Union. The limits of quantification were 1000, 750, 150, and 25 µg/kg for liver, kidney, muscle, and fat respectively. No information was provided regarding ovine milk.

**Conclusions and recommendation**

Having considered that:

- an ADI of 0.010 mg/kg bw (i.e. 0.6 mg/person) was established for imidocarb,
- MRLs have been established for cattle based on the percentage of total residues present as imidocarb in bovine tissues, after subcutaneously administration of 3 mg/kg bw $^{14}$C-imidocarb dipropionate, was as follows: liver 68%; kidney 88%; muscle 88%; milk 77%; data were not available for fat and so a factor based on the lowest ratio in liver was applied (68%),
- pharmacokinetics of imidocarb are similar in cattle and sheep,
- imidocarb was retained as the marker residue in ovine tissues,
- imidocarb was also the major component of the residues in ovine liver and kidney; the data suggested that the relationship between marker and total residues would be the same as for bovines,
- a validated routine analytical method is available for the monitoring of residues in ovine tissues;

the Committee for Veterinary Medicinal Products recommends the inclusion of imidocarb 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 |
|---|---|---|---|---|---|
| Imidocarb | Imidocarb | Ovine | 300 µg/kg<br>50 µg/kg<br>2000 µg/kg<br>1500 µg/kg | Muscle<br>Fat<br>Liver<br>Kidney | Not for use in sheep from which milk is produced for human consumption |

Based on these MRLs, and considering the intake from bovine milk, the daily consumer intake of total residues would represent approximately 97% of the ADI.