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

EMEA/MRL/844/02-FINAL
July 2002

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

TRICHLORMETHIAZIDE
(Extension to dairy cows)

SUMMARY REPORT (2)

1. Trichlormethiazide (6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadazine-7-sulfonamide 1,1-dioxide) (CAS 133-67-5) is a diuretic and anti-hypertensive agent from the benzothiadiazide class which is used in veterinary medicine in cattle, sheep, goats, pigs and horses, at the following therapeutic regimen: a single intramuscular dose of 0.4 mg/kg bw followed by two oral doses of 0.8 mg/kg bw given 12 and 36 hours after the first administration.

   Trichlormethiazide is also used in humans in the United States as a diuretic and anti-hypertensive substance but not in the European Union. The usual dose is 2 to 4 mg twice a day (i.e. approximately 0.033 to 0.066 mg/kg bw/day).

   The CVMP previously assessed the data available for trichlormethiazide and established an ADI of 0.005 mg/kg bw, based on a NOEL of 1 mg/kg bw/day for reduction of haematocrit in male rats in a 3-week repeated-dose study and a safety factor of 200. The safety factor of 200 was used because of the short duration of the study. Trichlormethiazide is currently included into Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table

Pharmacologically active substance(s)	Animal species	Other provisions
Trichlormethiazide	All mammalian food producing species	Not for use in animals from which milk is produced for human consumption

   An application has now been submitted for the extension of MRLs for trichlormethazide to allow use in cattle producing milk for human consumption.

2. For the initial assessment of trichlormethiazide, the following pharmacokinetic data were available. The benzothiadiazides are rapidly absorbed from the gastrointestinal tract. Chlorothiazide, a substance related to trichlormethiazide, is distributed throughout the extracellular space and does not accumulate in tissues other than the kidney. The drug passes readily through the placental barrier to the foetus. They are rapidly excreted within 3 to 6 hours. Chlorothiazide does not undergo metabolic alteration in the body.

   In a cross-over pharmacokinetic study, 10 ruminating calves (5 animals per sex) received three administrations of trichlormethiazide at the dose rate of 0.4 mg/kg bw via intravenous, intramuscular and oral routes, with a two-week wash-out period between each administration. The non-compartmental analysis of the concentration-time data after intravenous injection showed that the elimination half-time was short (1.22 hours) and the mean residence time was 1.43 hours. The mean body clearance was 5 ml/kg.min and the volume of distribution at the steady state was 388 ml/kg. This low value for the volume of distribution indicates that trichlormethiazide is not widely distributed. After the intramuscular administration, the highest concentration in plasma, 195 µg/l, was measured 1.7 hours after the administration; the mean

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.eu.int http://www.emea.eu.int

bioavailability was close to 75% and the half-time of elimination was in the magnitude of 3 hours. Following oral administration, trichlormethiazide could be detected in 4 out of the 10 calves, the oral bioavailability was 14%.

In humans, after an oral administration of 66 µg/kg bw of trichlormethiazide, 60% of the parent compound was recovered in the urine 24 hours post dose.

3. From the pharmacokinetic study carried out in bovine, it was shown that the volume of distribution was low, indicating that trichlormethiazide is not widely distributed. Following intramuscular administration, although the bioavailability was close to 75%, it can be assumed that 30 hours after administration, as the half-time of elimination was in the magnitude of 3 hours, the total administered dose of trichlormethiazide will be eliminated. Consequently, as the intramuscular administration is the first step of the three repeated administrations (one intramuscular and two oral administrations over a 36-hour-period) the residues at the injection site do not present any unacceptable risk for the consumer under the proposed conditions of use.

4. Following oral administration, only a low fraction of trichlormethiazide is absorbed (oral bioavailability of 14.2%). Therefore, depletion studies in the target species, in tissues other than milk, were not considered necessary and it can be assumed that consumers are most unlikely to encounter residues of trichlormethiazide in edible tissues from treated animals.

5. A GLP-compliant residue study in milk was provided. Twenty dairy cows were treated orally with trichlormethiazide on three consecutive days at a dose of 0.72 to 0.88 mg/kg bw on the first day followed by a dose of 0.36 to 0.44 mg/kg bw on days 2 and 3 of treatment. Milk was collected twice daily for a period of 4 days. Milk samples were analysed for trichlormethiazide using a HPLC method with MS/MS - detection (limit of detection: 4.8 µg/kg; limit of quantification:
50 µg/kg). None of the milk samples showed concentration values above the limit of quantification. The highest detectable trichlormethiazide concentrations were 27.4 µg/kg (mean: 15.1 µg/kg) and 21.8 µg/kg (mean: 10.5 µg/kg) at the 1st (4 hour) and the 2nd (16 hour) milking after the end of treatment, respectively. At the 3rd milking (28 hour) residue concentrations were below the limit of detection in 17 out of 20 milk samples.

6. Considering the highest detectable milk concentration value of 27.4 µg/kg in the 1st milking, the estimated daily intake of trichlormethiazide from 1.5 l milk is 41.1 µg (0.685 µg/kg bw), or 13.7% of the ADI. Since this intake represents only a small portion of the ADI, there is a sufficient margin of safety to protect consumers.

Conclusions and recommendation

Having considered that:

- trichlormethiazide is used in individual animals only for infrequent and non-regular treatment,
- the animals treated are unlikely to be sent for slaughter immediately after treatment,
- trichlormethiazide is quickly eliminated,
- trichlormethiazide residues in milk were low and the estimated daily intake represented only a small portion of the ADI;

the CVMP considers that there is no need to establish MRLs for milk for trichlormethiazide and recommends the modification of the existing entry in Annex II of Council Regulation in accordance with the following table :

Pharmacologically active substance(s)	Animal species	Other provisions
Trichlormethiazide	All mammalian food producing species	