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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

TRICHLORMETHIAZIDE

SUMMARY REPORT (1)

1. Trichlormethiazide (6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadazine-7-sulfonamide 1,1-dioxide) 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.

   Trichlormetiazide also used in humans in 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).

2. Benzothiadiazide derivatives exert their diuretic effect at the distal convoluted tubule and collecting duct. Although the exact mechanism is not fully understood, there is some evidence that the effect of diuresis is due to the specific inhibition of the chloride-dependent sodium transportation in the distal tubule, resulting in a decreased reabsorption of sodium and in the excretion of urine with increased concentrations of sodium, chloride, magnesium and potassium ions. Furthermore, the r-absorption of water in the collecting ducts is inhibited. In dogs a significant diuretic and natriuretic effect can be obtained after oral administrations of doses as low as 0.01 mg/kg bw.

3. 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 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 were recovered in the urine 24 hours post dose.

4. For trichlormethiazide, the oral LD_{50} values were higher than 5000 mg/kg bw and the intraperitoneal LD_{50} values were higher than 2000 mg/kg bw in mice and in rats.

5. In a short-term repeated dose toxicity study, four groups of 20 specific pathogen free rats were treated orally once daily five times a week for three consecutive weeks with trichlormethiazide at 0, 1, 50 and 100 mg/kg bw. A statistically significant reduction in haematocrit was observed in male rats treated with 50 and 100 mg/kg bw. No other change was apparent in haematological observations. The NOEL was 1 mg/kg bw.

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6. Six dogs received 1 g/kg bw of trichlormethiazide on 7 days per week for approximately 3 weeks. No adverse clinical signs, no significant gross or histopathological changes were observed.

7. Four groups of 50 rats received trichlormethiazide in the diet at doses of 0, 50, 1 000 and 10 000 mg/kg feed (corresponding approximately to 5, 100 and 1000 mg/kg bw/day) for a period of 16 weeks. A significant increase of kidney weights was observed in the female animals which had received the highest dosage. A significant decrease of total leukocytes counts was also reported after 13 weeks of treatment of the females with the highest level, but these counts remained within normal limits and no effect on any one leukocytic element was observed. A non-significant decrease of the pituitary weights was reported in the female rats treated with 100 mg/kg bw. No morphological changes were found in the kidney and pituitary tissues. The NOEL was 100 mg/kg bw.

8. In a one-year repeated dose toxicity study, rats of both sexes were treated with trichlormethiazide at dietary dose levels of 50, 1 000 and 10 000 mg/kg feed (doses expressed in mg/kg bw not stated). No significant clinical, histopathological or haematological differences were observed.

   In another one-year repeated dose toxicity study, 24 dogs received trichlormethiazide orally at doses of 0, 0.5, 50 or 500 mg/kg bw/day. In the 500 mg/kg bw dose group, a statistically significant degree of hypokalemia was reported in males. This effect was dose related as it had been reported in all groups, but the variations were not significant for the two lowest dosage groups and should be related to the pharmacological properties of the compound. A LOEL of 50 mg/kg bw/day was retained for this study.

9. In a reproduction study in rats, 20 females and 10 males received orally 20 mg/kg bw of trichlormethiazide. After 60 days of treatment, they were mated. The offspring was studied for 12 days. The parents were mated again and the second offspring were studied for 21 days. The parents were treated before and after gestation and during suckling. No adverse effects were reported at 20 mg/kg bw/day.

10. A published documentation indicates that trichlormethiazide gave negative results in the *Salmonella* microsomal assay and positive results in a chromosomal aberration test in Chinese hamster lung cells.

    Mutagenicity tests carried out according to current guidelines, two *in vitro* tests (*Salmonella* microsomal assay and Mouse lymphoma TK assay) and one *in vivo* test (micronucleus test in mice). Trichlormethiazide gave negative results in the *Salmonella* microsomal assay. In the Mouse lymphoma TK assay, in one replicate at a cytotoxic concentration (2000 µg/ml), a statistically significant increase in the mutant frequency was reported in absence and with metabolic activation. Although this increase was not dose-related and slightly lower than twice the number of mutants of the control groups, this result remained questionable. In one *in vivo* micronucleus test in mice after intraperitoneal administrations of trichlormethiazide at dosage up to 2000 mg/kg bw, trichlormethiazide gave a negative result. The *in vitro* positive result was found to be expected at high concentrations and therefore it was concluded that there was no evidence for mutagenicity of residues of trichlormethiazide.

11. In humans, trichlormethiazide produces diuresis within about 2 hours, reaching a maximum in about 6 hours and lasting about 24 hours. High oral doses of trichlormethiazide of 500 µg/kg bw (7.5 times the highest therapeutic dose) induced nausea, vomiting, cyanosis and pulmonary oedema. At the same dose, changes in plasma blood levels of sodium, chloride and potassium and in biochemical parameters (total protein, bilirubin, cholesterol) were reported.

12. From the available toxicological data provided, a toxicological ADI of 0.005 mg/kg bw could be established, based on a NOEL of 1 mg/kg bw/day from the 3-week toxicity study carried out in rats, applying a safety factor of 200. The safety factor of 200 is justified by the fact that the study retained to calculate the toxicological ADI lasted only 3 weeks. From the pharmacological data provided, significant diuretic and natriuretic effects were seen in dogs after oral administrations of doses as low as 0.01 mg/kg bw. This dose is 3-fold lower than the lowest therapeutic dose recommended in humans. Having regard to the use of this compound in veterinary medicine and to its pharmacokinetic profile, it was concluded that further toxicity or pharmacological studies were not necessary to complete the safety profile of trichlormethiazide.

13. 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.

14. Following oral administration, only a low fraction of trichlormethiazide is absorbed (oral bioavailability of 14.19%). Therefore, depletion studies in the target species 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. However, no conclusion could be drawn for milk.

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 poorly absorbed after oral administration in the target species and is quickly eliminated;

the CVMP considers that there is no need to establish MRLs for trichlormethiazide and recommends its inclusion 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	Not for use in animals from which milk is produced for human consumption