



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

MENBUTONE

SUMMARY REPORT

1. Menbutone [$C_{15}H_{14}O_4$] [beta-(1-methoxy-4-naphthoyl) propionic acid or genabilic acid] is a choleric compound which is used in veterinary medicine at a dose rate up to 10 mg/kg bw by parenteral (intravenous or intramuscular) route in bovine, ovine, caprine, porcine and equine species.
2. Menbutone increases the excretion of the bile, the gastric and the pancreatic juice into the gut by twice to five fold the normal secretion and stimulates the function of the gastrointestinal tract.
3. The pharmacokinetics of menbutone have been studied in rats and in cows after a single oral or intravenous administration of 10 mg/kg bw ^{14}C -labelled menbutone.
 - In rats, absorption of ^{14}C -menbutone from the gastrointestinal tract was almost complete. About 50-60% of the orally administered radioactivity was eliminated via the urine after 4 to 8 hours. After 24 hours, 79% was excreted via the urine and 4.4% via the faeces (most of the radioactivity was found in a unidentified metabolite). Between 20 and 30% of the intravenously administered radioactivity were excreted in the bile.
 - In cows one hour after intravenous injection, 20 mg/l of menbutone were measured in plasma. After 8 hours, the plasma concentrations were lower than 1 mg/l.

40.4 % of the radioactive oral dose and 12% of the intravenous dose were excreted in the urine within 24 hours. Menbutone represented 25 % of urinary radioactivity.

In milk, a maximum concentration of 0.7 to 0.8 mg/l was reported at about five hours after injection. At or before 14 hours, menbutone concentrations had fallen to 0.1 mg/l or less.
4. After a combined intramuscular administration of ^{14}C -menbutone (2 μ Ci) and menbutone at 10 mg/kg bw to rats, the tissue contents of menbutone and its metabolites at 24 hours after the administration were less than 0.06 mg/kg in muscle and fat, 0.16 mg/kg in liver and 0.2 mg/kg in kidneys, the compound being analysed by spectrofluorometry.
5. The acute toxicity of menbutone was low, the oral LD_{50} values being 1500 mg/kg bw in mice and 3000 mg/kg bw in rats, respectively. The intravenous LD_{50} value was 400 mg/kg bw in mice.
6. Ten rats/sex/dose level were dosed orally with 0, 30, 100, 300 and 1000 mg/kg bw of menbutone diethylamine salt 5 times weekly over a period of 20 weeks. Clinical signs of toxicity, including cyanosis and decreased respiration, were reported in 3 rats treated with 300 mg/kg bw and in 14 rats treated with the highest dose. High mortality was observed in the two highest dose level groups. Degeneration of tubulus epithelium was seen in the kidneys of animals that died before study termination. A significant increase in the relative liver weights was reported in rats treated with 100, 300 and 1000 mg/kg bw. A NOEL of 30 mg/kg bw was established.
7. Eight calves and eight pigs were given an intramuscular injection of menbutone in a dose of 10 mg/kg bw. Three days after the injection muscle necrosis at the injection site, haemorrhage and oedema in the adjacent tissue were reported in calves and muscle necrosis at the injection site was noted in pigs.

In another study, eight pigs received two injections of menbutone at 10 mg/kg bw, one into the left side of the neck 28 days before autopsy and the other into the right side of the neck 14 days before. Microscopically, a large well defined area of necrotic muscle tissue surrounded by a zone of fibrous or granulation tissue was found and this necrosis did not heal completely during the period of 28 days.

8. Fifteen pregnant sows at 40-80 days pregnancy, were injected intramuscularly with 1 g of menbutone 2 times with 12 hours interval. Animals were inspected each day for ten days and no evidence of an adverse effect on reproduction nor any signs of abortion were reported.

There is no other information on reproductive toxicity in laboratory animals.

9. Menbutone did not show any evidence of mutagenicity in the Ames test, in the mammalian cell gene mutation assay and in the mouse micronucleus test.
10. In a clinical trial, the effect of menbutone on serum cholesterol was investigated in 64 hospitalized patients, presenting coronary insufficiency. The oral level dose used was 1500 mg per day (divided into 3 intakes) per person during 3-4 weeks. No clinical adverse effects were noted.
11. An ADI of 0-0.060 mg/kg bw, i.e. 3.6 mg per person per day can be established from the NOEL (obtained in the 20-week toxicity study in rats) of 30 mg/kg bw using a safety factor of 100 and an additional factor of 5 due to the low number of animals and the lack of teratogenicity studies.
12. Twenty-four hours after the intramuscular administration of 10 mg/kg bw to pigs, the amount of residues was inferior to 0.5 mg/kg in muscle and fat and was approximately equivalent to 0.9 mg/kg in liver and kidneys (1 animal; spectrofluorometric method). However, the concentrations measured in two animals fell to 0.07 mg/kg in liver and 0.1 mg/kg in kidney, 48 hours post administration.

Seventy-two hours after the end of repeated administrations of 20 mg/kg bw of menbutone once a day for 3 days, the following levels of menbutone were measured in pig tissues : 0.007-0.008 mg/kg in muscle and fat and close to 0.030 mg/kg in liver and kidney. At the injection site, the level reached 0.320 mg/kg.

An oral repeated administration of 10-12 mg/kg bw twice a day for 4 months was carried out in pigs. At the end of the treatment, the tissues were collected and analysed by UV spectrophotometry. In fat and muscle, the concentrations of menbutone were close to 0.2 mg/kg, in the liver and kidney they reached 5 mg/kg.

13. In one calf, 24 hours after an intramuscular administration of 10 mg/kg bw, the muscle and fat contained less than 0.3 mg/kg of residues, the residues being assayed by a spectrofluorometric method). These concentrations were 0.8 mg/kg in liver and 0.5 mg/kg in kidney. Forty-eight hours later, the menbutone concentrations of samples collected from 2 animals were less than 0.03 mg/kg except for kidneys (0.1 mg/kg).

In another study, seventy-two hours after the end of repeated administrations of 20 mg/kg bw of menbutone once a day for 3 days, the following levels of menbutone were measured in edible tissues of the two cows treated : 0.008 mg/kg in muscle and fat, 0.027 mg/kg in liver and 0.033 mg/kg in kidney. At the injection site, the level reached 0.260 mg/kg.

Six days after administration of 3 g of menbutone by intramuscular route to two bull-calves, menbutone could not be detected in edible tissues. Only at the site of the injection was a concentration higher than the control animal (0.10-2.0) detected.

14. One lactating cow was treated with an intramuscular administration of ^{14}C -menbutone at the dose level of 10 mg/kg bw. The ratio unchanged menbutone (0.182 mg/kg) on total residue (2.05 mg/kg) represented 8.9% in the milk collected at 24 hours.

Fourteen hours after intravenous administration of 10 mg/kg bw to cows, menbutone levels had fallen to 0.1 mg/kg or less.

In milk from goats treated by intramuscular administrations of 10 mg ^{14}C -menbutone/kg bw, the concentrations of residues in milk was 0.03 mg equivalent menbutone/l, 72 hours after the administration.

Recommendations and conclusion :

Having considered the criteria laid down by the Committee for inclusion of substances in Annex II of the Council Regulation (EEC) No 2377/90, in particular that :

- menbutone is only administered to a small number of animals or individual animals which are not intended for immediate slaughter,
- the total daily intake is 3.6 mg per person of 60 kg bw per day, resulting from the ADI of 0.06 mg/kg bw/day,
- menbutone is rapidly eliminated (the elimination half-life being estimated as 8 hours after a parenteral administration),
- the assumed intake after 48 hours constitutes an insignificant fraction of the established ADI,

the Committee considers that there is no need to establish an MRL for menbutone and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table :

Pharmacologically active substance(s)	Animal species	Other provisions
Menbutone	Bovine, ovine, caprine, porcine, equidae	