



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ERGOMETRINE MALEATE

SUMMARY REPORT

1. Ergometrine is a naturally occurring alkaloid found in ergot (*Claviceps purpurea*). It is classified as a water-soluble lysergic acid derivative, and is an orally-active stimulant of uterine contractions. The maleate salt (ergometrine maleate) exhibits greater stability than the free base and is the usual form in which the alkaloid is used in medicinal products.

It is used in veterinary medicine in the control of postpartum uterine haemorrhage, removal of fluid from atonic uteri, to prevent pro-lapsed uteri, and judiciously in terms of timing to aid in suturing the uterus after caesarean section or in replacing an everted uterus. Dose regimens are: cows and mares: 2 to 5 mg/animal (intravenously or intramuscularly); ewes, goats and sows: 0.5 to 1 mg/animal (intramuscularly).

In human medicine, it is used orally and parenterally in the prevention and treatment of postpartum haemorrhage caused by uterine atony and for the stimulation of uterine involution. Usual oral doses are 500 µg 3 times daily up to 1.8 mg daily (approximately 0.03 mg/kg bw).

Ergot alkaloids have been reported to be present in flour from rye, wheat and barley in amounts ranging from 0.01 to 2.36 mg/kg flour. EU legislation restricts the maximum percentage of ergot tolerated in flour to 0.1%. Total daily human intake of ergot alkaloids from contaminated foodstuffs of plant origin has been estimated as up to 7.8 µg/person.

2. Judging from the rapid onset of action, ergometrine maleate is rapidly absorbed (after oral administration and by intramuscular injection) and rapidly effective about 10 minutes after oral dosing and 7 minutes and 1 minute after intramuscular and intravenous injections, respectively. The action persists maximally for about 1 hour and gradually lessens over a period of several hours. Elimination appears to be principally via the bile after metabolism in the liver. Judging from the relative duration of action, ergometrine maleate is metabolised and/or eliminated rapidly.
3. Limited information is available on the pharmacokinetics of ergometrine. Ergometrine, like the closely related methylergometrine, is generally rapidly and extensively absorbed after oral administration to humans (6 males) after a light breakfast with uncontrolled amounts of coffee or tea. However, large interindividual variations of the oral bioavailability are observed (average: approximately 80%, range: 34 to 117%), which may have been influenced by differences in the liquid intake. It is also excreted reasonably fast, the elimination half-life after oral administration being in the order of 2 hours. A second study in human volunteers (6 per substance, cross-over design), investigated pharmacokinetics and bioavailability of comparable doses of ergometrine and the closely related compound methylergometrine after oral and intravenous administration. The following doses were used: ergometrine maleate - 0.2 mg/person by oral route, and 0.075 mg/person by intravenous route (equivalent to 0.147 mg and 0.055 mg base/person, respectively); methylergometrine maleate - 0.125 mg/person by oral route and 0.2 mg/person by intravenous route (equivalent to 0.095 mg and 0.152 mg base/person, respectively). The results confirm the mean oral bioavailability of ergometrine as 80.7% with large variations (42.7% CV). A similar result was obtained for methylergometrine with a mean oral bioavailability of 84.9% (43.8% CV).

The following pharmacokinetic parameters were observed for ergometrine and methylergometrine, respectively, after intravenous administration: a distribution half-life of 0.16 and 0.19 hours, an elimination half-life of 2.57 and 1.85 hours, a total body clearance of 32.6 and 32.2 and steady-state volumes of distribution of 82.0 and 71.5 litres.

Limited data are available on the metabolism of ergometrine in rats after intravenous administration, however only bile was studied. The major route of biotransformation (after 3 mg/kg bw) is hydroxylation at position 12 of the ring system, leading to the metabolites 12-hydroxy-ergometrine and its isomer 12-hydroxy-ergometrinine, which are then conjugated to glucuronic acid and excreted in bile. Following a larger dose (45 mg/kg bw) some unchanged parent compound and its isomer ergometrinine as well as glucuronides of ergometrine and ergometrinine (thought to be modified in the propanolamide side chain, but confirmation lacking) are observed. Trace amounts of two further isomeric pairs of metabolites less polar than ergometrine (not further identified, but considered likely to be N-demethylation products) are observed.

No data on total excretion of ergometrine are available.

In addition, information on the excretion of ergometrine in milk is lacking. However, for the closely related substance methylergometrine with similar pharmacokinetic characteristics in humans, only limited excretion into breast milk is reported, again with large interindividual variation. Eight women received ergometrine maleate at an oral dose of 0.125 mg/person (mean dose of 3.7 µg/kg bw) 3 times a day for several days, i.e. a total daily dose of 0.375 mg/person. On day 5 the dose of one administration was doubled to 0.25 mg/person and the concentration of ergometrine in milk was studied 1 and 8 hours after administration. After 1 hour ergometrine was detected in milk of 4 out of 8 patients at concentrations ranging from 0.6 to 1.3 µg/l. Eight hours after treatment only 1 out of 8 samples contained quantifiable amounts of ergometrine, i.e. 1.2 µg/l (limit of detection 0.5 µg/l).

4. Early signs of gangrenous ergotism in animals are lameness, painful stance or treading and stamping of the feet, and cool extremities. There is a well-defined, constricted band between normal skin and distal parts of the limbs. The ears, nose and tail are also affected. The distal extremities, tail, ears, and nose slough away, leaving a clean surface that may ooze serum and become encrusted. Secondary bacterial infection occurs readily.
5. Rats received ergometrine maleate in their diet for 4 weeks at doses of 0, 2, 10, 50 and 250 mg/kg feed, corresponding to mean daily intakes of 0, 0.2, 1, 5 and 25 mg/kg bw. At the high dose level plasma thyroxin levels (thyroxin and free thyroxin, reaching statistical significance in males only) and glucose levels (reaching statistical significance in females only) were decreased, while some organ weights (heart, liver, ovaries, kidneys) were increased. In male, but not in female, rats of the 250 mg/kg feed and 50 mg/kg feed dose groups, a dose related increase in the incidence of enlarged mediastinal and, to some extent, parathymal lymph nodes was observed. At histological examination an increase in glycogen storage in the liver was seen. At 50 mg/kg feed plasma thyroxin (free thyroxin) and glucose levels were decreased in males and females, respectively. Prolactin levels in serum of animals of the 250 mg/kg feed and the 50 mg/kg feed dose group were also markedly decreased, but this effect was studied in too few animals to allow statistical analysis. The dose of 10 mg/kg feed, corresponding to 1 mg/kg bw, was retained as the NOEL of this study.
6. While no further studies on repeated dose toxicity, and no studies on reproductive toxicity including embryotoxicity/foetotoxicity and tolerance in target species were presented, submission of such studies was not considered necessary as ergometrine maleate has a long history of safe use in human and veterinary medicine and is rapidly inactivated.
7. While no specific mutagenicity or carcinogenicity studies were provided and while the Committee was made aware of a publication identifying ergometrine as an inducer of sister chromatid exchanges (SCE) in Chinese hamster ovary (CHO) cells *in vitro* no further information was considered necessary when taking into account the very limited use of the substance and its rapid inactivation.
8. Ergometrine is used in human medicine, by oral or intravenous route, for prevention and treatment of postpartum haemorrhage. Adverse effects include nausea, vomiting due to a direct central emetogenic effect, and, particularly after rapid intravenous administration, hypertension. Symptoms of vasoconstriction occur less frequently than with ergotamine tartrate, another ergot alkaloid used in human medicine.

Chronic poisoning with ergot alkaloids, or ergotism, has been reported after therapeutic overdose of other ergot alkaloids, e.g., ergotamine, or after intake of contaminated grain or flour (in one instance following consumption of grain containing up to 0.75% ergot). Ergotism in humans is characterised by severe circulatory disturbances, initially present as tingling and numbness of extremities, with muscle pain, sometimes culminating in gangrene in fingers and toes.

9. The information provided on the possible presence of residues of ergometrine in colostrum and milk was poorly addressed, and no precise information was given regarding the pharmacokinetic profile of ergometrine in milk after the administration to lactating food producing animals. However, animals are treated at parturition only. From published information concerning cattle it is evident that ergot alkaloids including ergometrine are rapidly eliminated in urine and faeces (within a few hours). Due to the characteristics of colostrum, normal commercial production of milk for human consumption does not begin until 3 to 4 days postpartum. Thus the presence of ergometrine residues in milk due to treatment of individual animals is perceived as very unlikely.

Conclusions and recommendation

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

- ergometrine maleate is administered very occasionally, on parturient females only,
- treated animals are unlikely to be sent for immediate slaughter,
- ergometrine maleate has a short duration of action on the target organ (uterus) and is rapidly eliminated (within a few hours);

the Committee concludes that there is no need to establish an MRL for ergometrine maleate 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
Ergometrine maleate	All mammalian food producing species	For use in parturient animals only