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

EMEA/MRL/323/97-FINAL
January 1998

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

BUTORPHANOL TARTRATE

SUMMARY REPORT

1. Butorphanol tartrate, a synthetic opioid agonist-antagonist analgesic, is used as an analgesic and sedative compound in horses. It is administered by intravenous route at recommended doses of 0.025 mg/kg bw for sedative and 0.1 mg/kg bw for analgesic purposes. It is also used in cats and dogs.

   In humans, butorphanol tartrate is used for the relief of moderate to severe pain and as an adjunct in anaesthesia. For the relief of pain, butorphanol is given in doses of 1 to 4 mg every 3 or 4 hours by intramuscular injections. It may also be administered in doses of 0.5 to 2 mg by intravenous injection. It has also been given as a nasal spray in the usual dose of 1 mg, repeated after 60 to 90 minutes if necessary.

2. The active form is the levo isomeric form which has a potency approximately 5 times stronger than that of morphine. It produces its effects by binding to opiate receptors. It has competitive antagonist activity at the μ-receptors, and agonist activity at κ– and σ-receptors.

3. The pharmacological properties of butorphanol tartrate were studied in several laboratory animal species for its analgesic and narcotic antagonist activities, for its effects on central nervous system, on the cardio-respiratory system and on behaviour after intravenous, subcutaneous and oral administrations. The doses tested in vivo ranged from 0.03 to 100 mg/kg bw for subcutaneous injections and from 2 to 10 mg/kg bw for oral administrations. In the phenylquinone writhing test in rodents, doses of levo-butorphanol of 0.041 mg/kg bw administered by subcutaneous route or of 2.1 mg/kg bw by oral route induced 50% reduction in writhing. The data provided were insufficient to retain an oral pharmacological NOEL (lower than 2 mg/kg bw). After administration to monkeys of 0.03 mg/kg bw by subcutaneous route, 1 of 7 animals had a positive reaction in a behaviour test.

4. In rats, after oral (gavage) administrations of ^{3}H-butorphanol at doses ranging from 1.6 mg/kg bw to 640 mg/kg bw expressed in terms of butorphanol base, 25 to 40% of the total radioactivity was recovered in urine within 96 hours post treatment, the remaining part being recovered in faeces. Three metabolites were identified in urine (hydroxybutorphanol, norbutorphanol and another unidentified metabolite, no percentages given). Both conjugated butorphanol and free butorphanol, accounting for 3% of the total urinary radioactivity, were also found. These metabolites were also reported in monkeys after oral administration of 3.7 to 4.4 mg/kg bw of radiolabelled compound.

   After intravenous administration of non-radiolabelled butorphanol at doses ranging from 0.25 mg/kg bw to 0.5 mg/kg bw (dogs, rabbits, cows), the half-life of elimination were less than 2 hours.

   In a pharmacokinetic study conducted in horses, butorphanol tartrate was administered by intravenous route at doses of 0.1, 0.2 and 0.4 mg/kg bw as butorphanol base. The clearance values were in the magnitude of 0.50 l/h·kg and the half-life of elimination ranged from 3.0 to 4.4 hours. Fifteen minutes after the intravenous administration of 0.1 mg/kg bw of butorphanol, the plasma concentrations were 0.5 μg/ml and they declined to 0.005 μg/ml at 240 minutes post injection.

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In humans, after intravenous administration of 1 mg ^{3}H-butorphanol tartrate or intramuscular administration of 2 mg, it was shown that butorphanol was rapidly distributed and had a plasma half-life of about 3 hours. In plasma, after intramuscular administration, butorphanol peak levels of 0.001 to 0.002 µg/ml occurred at 1 to 2 hours post injection whereas for hydroxybutorphanol peak levels of approximately 0.0005 µg/ml were observed at 4 to 6 hours and remained constant until 8 hours post injection. After intravenous or intramuscular administration, 71 to 72% of the administered radioactivity was excreted within 96 hours. In urine, 50% of the radioactivity excreted was present as hydroxybutorphanol, 6% as norbutorphanol and about 13% as the parent compound (free and conjugated). In plasma 83% of butorphanol is protein-bound.

In a series of 3 crossover studies conducted in humans (9 to 12 volunteers per group), the absorption of butorphanol was calculated after administrations of doses of 2 mg butorphanol tartrate intravenously and either transnasally, sublingually or buccally. The elimination half-life of butorphanol was about 3 to 5 hours and was independent of the administration route. Mean bioavailabilities of sublingual tablets and buccal disk formulations were 19% and 29% respectively but for the transnasal administration the value rose significantly to 70%.

In another study, it was shown that butorphanol after oral administration undergoes extensive first-pass metabolism so that the bioavailability of butorphanol after oral administration is only 5%.

5. The oral LD_{50} of levo-butorphanol tartrate was higher than 100 mg/kg bw in rats. The intravenous LD_{50} was 32 and 20 mg/kg bw in male mice and male rats, respectively. The subcutaneous LD_{50} was 300 and 620 mg/kg bw in male mice and male rats, respectively. Clinical signs of toxicity consisted in ataxia, a slowing in heart rate followed by a decrease in activity and a loss of righting reflex before the death.

6. Repeated dose toxicity studies after parenteral administration were conducted in rats, dogs and monkeys.

   In a 3-month toxicity study conducted in rats, levo-butorphanol tartrate was administered by subcutaneous route at doses of 0.5, 2.5 and 5 mg/kg bw/day expressed in terms of butorphanol base. As a dose-related increase in the average of the water intake was noted in all treated group and in absence of statistical test, no NOEL could be retained (lower than 0.5 mg/kg bw).

   In a 3-month toxicity study conducted in dogs, levo-butorphanol tartrate was administered by intramuscular route at doses of 0.1, 0.5 and 1 mg/kg bw/day expressed in terms of butorphanol base. In all treated group, a loss in the initial body weight was reported. This loss represents 1.2 to 4.2% in the intermediate dose group and 1.1 to 3.7% of the initial weight in the low dose group whereas in the control group, a mean gain of 2.1 to 2.5% was reported. A LOEL of 0.1 to 0.5 mg/kg bw/day can be retained for this study.

   In a 6-month toxicity study, monkeys received levo-butorphanol tartrate via intramuscular route at doses of 0.15, 0.75 and 1.5 mg/kg bw/day expressed in terms of butorphanol base. As only transient sedation effects were reported for all doses, it can be concluded that the intramuscular administrations of butorphanol did not induce adverse toxic effect up to 1.5 mg/kg bw.

   After subcutaneous or intramuscular administrations, most of the findings were related to the pharmacological properties of the test substance.

7. The tolerance of butorphanol tartrate in horses has been tested either after single or repeated administrations of increasing intravenous doses up to 10-fold the recommended dosage of 0.1 mg/kg bw. Butorphanol tartrate was well tolerated. Minor transient adverse effects related to the central nervous system and the gastrointestinal tract were reported.

8. In a first set of reproductive studies, levo-butorphanol tartrate was administered by subcutaneous route to animals at different stages of the reproduction. All dosages are expressed in terms of butorphanol base. In rats, the subcutaneous administrations of levo-butorphanol tartrate at doses of 0.5 and 2.5 mg/kg bw/day for 75 days prior to mating in males, and for 14 days prior to mating and throughout the gestation period and up to the lactation period in females, induced a significant decrease of the body weights of the parents and a lower survival index in pups. No NOEL was retained (lower than 0.5 mg/kg bw).

   In a second set of reproductive studies, butorphanol tartrate (stereosisomeric form and the real expression of the dosage not given) was administered by oral route to animals at different stages of the reproduction. Rats received doses of 10, 40 and 160 mg/kg bw/day of butorphanol tartrate for 63 days prior to mating for males, and for 14 days prior to mating and throughout the gestation period and up to the lactation period for females. At the highest dose, side-effects (alopecia, reduced number of successful conceptions) were reported in parents whereas 10 and 40 mg/kg bw/day were without effects. As the only adverse effect on foetuses observed at 10 and 40 mg/kg bw was a significant increase in mean foetal weight (3.96 g and 3.90 g in the 10 and 40 mg/kg bw groups versus 3.57 g in the control group) these dosages may be considered without toxicological relevance and a NOEL of 40 mg/kg bw/day can be retained for embryotoxicity.

9. In a first set of parenteral teratogenicity studies, three studies were conducted in rats (subcutaneous route), mice (subcutaneous route) and rabbits (intramuscular route). Whatever the species considered, levo-butorphanol tartrate was neither teratogenic nor embryotoxic at doses up to 1 mg/kg bw/day. However, a NOEL of 0.5 mg/kg bw/day for maternotoxicity was retained for rats, whereas 1 mg/kg bw/day was without effects in mice or in rabbits (doses expressed in terms of butorphanol base).

   In a second set of oral teratogenicity studies, two studies were conducted in rats and in rabbits. In rats the oral administration of butorphanol at doses of 10, 40 and 160 mg/kg bw/day did not induce toxic effects in dams and offspring. At doses up to 160 mg/kg bw/day, butorphanol tartrate was neither maternotoxic nor embryotoxic nor teratogenic.

   Rabbits were treated with oral doses of 15, 30 and 60 mg/kg bw/day. As a decrease of the pregnancy rate was reported at 60 mg/kg bw, 30 mg/kg bw/day was retained as the NOEL for maternotoxicity. Butorphanol tartrate at doses up to 60 mg/kg bw/day (doses expressed in terms of butorphanol base) is neither embryotoxic nor teratogenic when orally administered to rabbits.

10. In a peri- and postnatal study female rats received oral doses of 10, 40 and 160 mg/kg bw/day of butorphanol tartrate from day 15 of gestation to day 21 post partum. No adverse effects on the perinatal phase, delivery and postnatal life of animals were seen up to 160 mg/kg bw/day.

    Subcutaneous doses of 0.1 and 1 mg/kg bw/day of levo-butorphanol tartrate administered to female rats from day 15 of gestation to day 21 post partum did not induce adverse effects on the perinatal phase, delivery and postnatal life of animals.

11. Levo-butorphanol gave negative results in *in vitro* tests (Ames tests with *Salmonella typhimurium* and with *Escherichia coli*, in the Chinese hamster ovary cytogenetic assay and in DNA repair assay with WI-38 human fibroblasts). It was concluded that levo-butorphanol is unlikely to be a mutagenic compound.

12. Carcinogenicity studies were conducted in rats and in mice.

    Sprague-Dawley rats received butorphanol tartrate in the diet for 78 weeks at doses of 1 and 2 mg/kg bw/day. A significant increase in the incidence of squamous cell carcinoma of the skin was noted in males at the lowest dose (4 of 50 versus 0 of 75 in controls). Such effects were not reported for females and for males of the highest dose groups. As this effect was not dose-related and as because this tumour occurred spontaneously in old Sprague-Dawley rats, it can be concluded there was not evidence of carcinogenicity in rats.

CD-1 mice received butorphanol tartrate in the diet at doses of 0 and 60 mg/kg bw/day for one year, and at doses of 5, 15 and 60 mg/kg bw/day for 2 years, including a 60 mg/kg bw/day recovery group which was treated for the first 52 weeks. No carcinogenic potential in mice up to 60 mg/kg bw/day was reported.

13. In humans, the most frequent adverse effects of butorphanol are drowsiness, sweating, nausea, dizziness and vertigo. Prolonged use of butorphanol may lead to opioid dependence. It may precipitate withdrawal symptoms if given to patients who have recently used other opioid analgesics.

14. No data on the microbiological properties of butorphanol tartrate were provided. However, this information was not considered relevant for this compound.

15. As the oral bioavailability of this compound is low (less than 5%), it may be concluded that the use of butorphanol in horses is unlikely to result in residues in foodstuffs of animal origin at concentrations, which are pharmacologically relevant for the safety of consumers.

16. Based on a NOEL of 30 mg/kg bw/day retained from the oral teratogenicity study carried out in rabbits, and applying a safety factor of 100, a toxicological ADI of 0.3 mg/kg bw/day, i.e. 18 mg for a 60 kg person can be established. Considering the rapid elimination of butorphanol tartrate, this ADI value gives reassurance that no residues of butorphanol toxicologically relevant for the safety of the consumer should result from the use of the substance in horses.

Conclusions and recommendation

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

- butorphanol is used in a small number of individual animals for an infrequent and non-regular treatment,
- the treated animals are unlikely to be sent for slaughter immediately after treatment,
- the oral bioavailability in humans is low,
- after intravenous administration, butorphanol tartrate is rapidly eliminated with an half-life of 3.0 - 4.4 hours,
- the use of butorphanol in horses should not result in residues in food of animal origin at concentrations which are pharmacologically or toxicologically relevant for the safety of consumers;

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

Pharmacologically active substance(s)	Animal species	Other provisions
Butorphanol tartrate	Equidae	For intravenous administration only