



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

SUMMARY REPORT

LOBELINE

1. Lobeline is a piperidine-like alkaloid from *Lobelia inflata* with structural similarities to nicotine. In veterinary medicine lobeline as its hydrochloride is indicated for diagnostic purposes in food producing mammals during examination of the respiratory tract. Recommended are single doses of 0.1 mg/kg bw for intravenous and 0.2 mg/kg bw for intramuscular or subcutaneous injection.

Lobeline (as hydrochloride or sulfate) has been used in human and veterinary medicine for a long time as respiratory stimulant following parenteral application, and in humans additionally in combination with antacids as a smoking deterrent following oral administration.

2. Lobeline exerts nicotine-like effects on n-choline receptors, though less pronounced than nicotine itself. It has a differential affinity, the chemoreceptors of the aortic and carotid bodies being the most sensitive, followed by receptors of the autonomous ganglia, then choline receptors of neuromuscular junctions, while CNS cholinergic receptors are practically insensitive, even at toxic doses. The effects described in the following were observed in all species studied (laboratory animals, target species and humans).

The desired effect is an increase of respiratory frequency and tidal volume, as a result of the stimulation of the carotid body chemoreceptors. Following parenteral application this effect lasts a few minutes. Oral administration is ineffective. Minimal effective intravenous doses range from 0.015 mg/kg bw in horses to 0.1 mg/kg bw in dogs.

Parenteral doses slightly higher than those necessary for respiratory stimulation cause cardiovascular responses attributable to both the parasympathetic and sympathetic nervous system. Symptoms are bradycardia or arrhythmia and increase of pulmonary and systemic blood pressure. In dogs also minimal relaxation of bronchial musculature occurs. Much higher parenteral doses (>2-5 mg/kg bw in dogs) cause contractions of the gastrointestinal tract. CNS effects (convulsions) were only provoked by sublethal toxic doses (rats: 10 mg/kg bw intravenous; mouse: 12.5-25 mg/kg bw intravenous; 50-100 mg/kg bw subcutaneous).

3. Limited information on pharmacokinetics, metabolism and excretion in animals is available. The rapid onset of the respiratory stimulation within 3-12 min. after subcutaneous or intramuscular administration and rapid disappearance of the effects after 5-10 min. duration indicates rapid absorption and distribution of lobeline from the injection site.

Following oral administration (dose not given) of lobeline to laboratory animals no blood levels were detectable (< 1 µg/ml). This is attributed to limited oral absorption, but also to degradation by gastric acids (concomitant intake of antacids leads to detectable blood levels without respiratory or cardiovascular effects) and/or a significant first-pass effect (rectal administration is effective).

Lobeline rapidly disappears from the blood after intravenous administration (rats: < 1 µg/ml within 20-30 min). In rats, subcutaneous injection of 150 mg/kg bw resulted in plasma levels of 9 µg/ml after 10 min, with liver containing plasma levels, brain and fat 2-3 fold higher (reflecting the lipophilicity) and kidneys (stipulated major organ of excretion) sixfold higher concentrations of lobeline. No data for muscle tissue exist.

Unchanged lobeline as well as two metabolites, one of which has a phenolic structure, were detected in rat urine. Both metabolites were also detected in rat tissues.

- For mice LD₅₀ values of ca. 100 mg/kg bw, 55.3 mg/kg bw and 8 mg/kg bw are reported after subcutaneous, intraperitoneal and intravenous administration of lobeline. In rats an intravenous lethal dose of 17 mg/kg bw was observed.

Convulsant (CNS) effects of lobeline begin following single subcutaneous doses of 3060 mg/kg bw in mice, 5-10 mg/kg bw in dogs and 2-5 mg/kg bw in rabbits.

- Intraperitoneal treatment of rats with lobeline sulfate at a dose of 10 mg/kg for a period of 3 weeks resulted in increased general activity and changes in the electro encephalogram (EEG). Bodyweight, rectal temperature, tail flick response and motor coordination were not affected.
- Information on long-term toxicity, reproductive toxicity, carcinogenicity and other effects of lobeline is not available, but lobeline does not bear structural analogies to known carcinogens. During its use in human and veterinary medicine no indications of teratological effects have arisen.
- The mutagenic potential of lobeline gave negative results in a DNA-cell-binding assay in *E. coli*. Lobeline was not clastogenic in cultures of human lymphoblastoid cell lines, though a co-clastogenic interaction with ethyl alcohol was observed,
- The therapeutic doses for respiratory effects of lobeline in human medicine are 0.06 mg/kg intravenous or 0.1 mg/kg subcutaneous . An intravenous minimal effective dose of 0.03 mg/kg bw has been established for these effects. Subcutaneous doses of 0.06 mg/kg bw have no cardiovascular effects. A single oral dose of 2 mg/person (ca. 0.03 mg/kg) of buffered lobeline has the same effect on respiratory rate, pulse, blood pressure and skin temperature as a starch placebo.

Oral doses of 3 x 2 mg lobeline sulfate per person cause serotonin release from epithelial cells of the gastrointestinal tract without clinical symptoms. A subcutaneous dose 0.3 mg/kg bw infrequently results in vomiting.

The oral availability of lobeline sulfate given 3 times daily after a meal for a period of 6 days was tested in volunteers. Without antacids a daily dose of 6 mg lobeline sulfate per person is not detected in blood. In combination with a mixture of short and long acting antacids blood levels cumulate to values of 1.8 µg/ml on day 6 and falls below the concentration which can be reliably detected with the employed method (0.2 µg/ml) within the next 6 days.

The use of lobeline sulfate as a smoking deterrent at a daily oral dose of 6 mg (3 x 2 mg) per person and day (ca. 0.1 mg/kg bw) in combination with antacids is regarded as safe by the Unites States Advisory Review Panel. Due to the lack of data on long-term toxicity and carcinogenicity the duration of treatment was limited to 6 weeks.

Conclusions and recommendation:

Despite the missing information it does not appear that treatment of food producing animals with lobeline results in residues posing a risk to consumer safety.

Therefore 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 :

- Lobeline is of low oral bioavailability and low oral toxicity in humans;
- Lobeline is used infrequently as single parenteral administrations in individual animals not intended for immediate slaughter;
- the likelihood of consumer exposure to lobeline residues is very limited.

Lobeline is recommended for 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
Lobeline	All food producing species	