



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

BUTAFOSFAN

(Extension to lactating cows)

SUMMARY REPORT (2)

1. Butafosfan ([1-(butylamino)-1-methylethyl]-phosphonic acid) is an organic phosphorus compound used as a phosphorus source in cattle. The major indications are disorders of the metabolism especially in young animals. Butafosfan is also used to support the treatment of infertility, tetany and paresis as an adjunct to calcium and magnesium therapy. Butafosfan is administered as a single dose by intravenous route and the dose may be repeated daily if required. The maximum recommended dose is 5.6 mg/kg bw.

An ADI of 0.6 mg/kg bw (i.e. 36 mg/person), has been established by the Committee for Veterinary Medicinal Products (CVMP) for butafosfan by applying a safety factor of 100 to the NOEL of 60 mg/kg bw in a repeated dose toxicity study in dogs.

Currently, butafosfan is included in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Butafosfan	Bovine	For intravenous use only and not for use in animals from which milk is produced for human consumption

An application has now been submitted for an extension to bovine milk. The maximum recommended dose is 5.6 mg/kg bw as a single dose by intravenous route and the dose may be repeated daily if required.

2. A pharmacokinetic and milk residue study was performed where butafosfan was administered intravenously at a dose of 5.6 mg/kg bw to 10 lactating cows (5 low milk yield and 5 high milk yield). Blood and urine samples were taken and analysed for butafosfan by an LC-MS/MS method. Residues of butafosfan in milk were assayed at approximately 10 hour intervals over a period of 68 hours using a validated LC-MS/MS method.

Serum levels of butafosfan declined rapidly from the mean peak levels of 58 918 µg/litre for high yield cows and 42 482 µg/litre for low yield cows at the first sampling time (4 minutes) to 342 and 661 µg/litre for high and low yield cows, respectively, at 8 hours. At the later times of 24, 48 and 72 hours, the concentrations of butafosfan were below the limit of quantification (20 µg/litre) except for 2 cows in the low yield group, which had concentrations of 21 and 22 µg/litre. The decline in butafosfan concentrations in serum could be fitted to a three compartment model. The mean half-lives were 1.9 minutes for the initial phase, 38.7 minutes for the intermediate phase and 115.6 minutes for the terminal phase in high yield cows. The corresponding half-lives in the low yield cows were 6.7, 40.0 and 116.6 minutes, respectively.

Urinary excretion was rapid following dosing. A mean of 77% of parent compound was recovered in urine within the first 12 hours. The pharmacokinetic profile of butafosfan in lactating cows was very similar to that of non-dairy cattle.

The highest mean concentration of butafosfan was detected in milk collected at 6 hours post-dose (271 µg/kg). The mean concentration then declined to 91 µg/kg at 20 hours post-dose and 18 µg/kg at 30 hours post-dose. At the later milking times concentrations of butafosfan were less than the limit of quantification (10 µg/kg) or detection (1 µg/kg) of the analytical method.

3. An LC-MS/MS method has been developed to measure residues of butafosfan in bovine milk and the limit of quantification was 10 µg/kg.

Conclusions and recommendation

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

- a toxicological ADI of 0.6 mg/kg bw (i.e. 36 mg/person) has been established for butafosfan,
- butafosfan is used infrequently in a small number of individual animals,
- butafosfan is rapidly eliminated after intravenous administration to lactating cattle,
- at 6 hours after treatment, the amount of residues from milk likely to be ingested by consumers represents only a fraction (less than 1.5%) of the toxicological ADI and is not considered to be of any risk to the consumer;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for butafosfan in milk and recommends therefore that the current entry in Annex II of Council Regulation (EEC) No 2377/90 should be amended in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Butafosfan	Bovine	For intravenous use only