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

EMEA/MRL/244/97-FINAL
November 1997

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

BUTYLSCOPOLAMINIUM BROMIDE

SUMMARY REPORT

1. Butylscopolaminium bromide is a quaternary ammonium derivative of scopolamine. It is used in veterinary medicine in combination with metamizole and is administered by intravenous or intramuscular injection. It is used as a spasmolytic and analgesic in horses, cattle and pigs. The available dosage information is in horses 0.2 mg/kg bw (single intravenous dose) in cattle 0.3 mg/kg bw (single intravenous or intramuscular dose) in calves 0.4 mg/kg bw (twice daily for 3 days by intramuscular injection), and pigs 0.4 mg/kg bw (single intramuscular dose). It is also used orally in combination with antibiotics in horses, cattle, sheep, goats and pigs (0.4 mg/kg bw twice a day).

2. Butylscopolaminium bromide has similar pharmacological properties to the belladonna alkaloid derivatives such as atropine and scopolamine. However it is generally less potent than atropine. It antagonises the actions of acetylcholine mediated through the muscarinic receptor. It also has some antagonist effect at nicotinic receptors.

3. The pharmacology of butylscopolaminium was investigated in several species. Most of the studies were carried out over 20 years ago and in many cases it was not possible to draw any conclusions regarding NOELs or LOELs due to the poor design of the studies. However it was concluded that 1 and 3 mg/kg bw were NOELs for gastrointestinal tract motility and tachycardia, respectively, following oral administration to dogs.

4. Pharmacokinetic studies were carried out in rats, humans, cattle, horses and pigs. In all species, a C_{max} was achieved a few minutes after parenteral administration. Absorption after oral administration was very poor and was estimated to be only 2-8% of the administered radiolabelled compound in humans. In rats and in the target species, the substance was widely distributed in the tissues, with highest concentrations being found in the liver and kidney. In all species it was rapidly excreted. In humans, most of the administered dose (more than 60%) was excreted in the urine after parenteral administration and in the faeces (approximately 90%) after oral administration. The major component in the urine in rats, horses and humans was unmetabolised butylscopolaminium bromide.

5. Acute oral LD_{50} values of 849-1045, 1040 and 600-1500 mg/kg bw were established in mice, rats and dogs respectively. The substance was more toxic via the parenteral routes, reflecting the better absorption. Acute oral LD_{50} values of 546-610, 12.3-15.6 and 58-74 mg/kg bw were reported in mice following subcutaneous, intravenous and intraperitoneal dosing respectively. The overt signs of toxicity included reduced activity, lack of co-ordination, tremors and convulsions.

6. Repeat-dose toxicity studies were carried out in the rat, dog and primate. Most of the effects observed were associated with the pharmacological action of the substance. These included mydriasis, tremors, increased water intake and increased stomach contents. The increased stomach contents probably reflected the inhibitory effect of butylscopolaminium bromide on

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gastrointestinal tract motility. In the dog, no NOEL was established in studies which used the intravenous and intramuscular routes of administration, due to the mydriasis observed at the lowest doses used (2x1 mg/kg bw/day intravenously). There was no repeat-dose study in the dog using the oral route of administration.

7. In a 26-week study in the rat using the oral route (0, 10, 250, 1000 mg/kg bw/day), the only effect observed at 10 mg/kg bw was an increased water intake. Two deaths and effects associated with the pharmacological effects on the substance were observed at the next dose level of 250 mg/kg bw. However in a second 26-week study (0, 20, 65, 200 mg/kg bw/day), the NOEL was 65 mg/kg bw per day based on an increased water intake and increased stomach contents at the next dose level.

8. In a rat reproduction study 3 litters were bred from parents which received butylscopolaminium bromide in the feed (0, 50, or 200 mg/kg feed) from 60 days prior to mating. The pregnancy rate was very poor in all groups and no F2 generation was bred. There was no evidence of teratogenicity and butylscopolaminium bromide was not teratogenic in a study in the rabbit (0, 50, 200 mg/kg, days 6-16 of gestation) which employed inadequate group sizes. It was not possible to draw any conclusions regarding foetotoxicity, fertility or reproductive toxicity from these studies due to deficiencies in their designs.

   In a teratogenicity study, groups of mated female CD-1 mice were administered daily oral (gavage) doses of 0 (distilled water), 10, 100, 450 or 900 mg/kg bw per day of the closely-related substance, scopolamine hydromromide from day 6 to 15 of gestation. The dose levels were determined on the basis of the results from a preliminary study in which a dose of 1200 mg/kg bw caused excessive maternal mortality and embriotoxicity). The study used a three-replicate design with 10-17 mice assigned to each dose in each replicate, resulting in a total of 35-45 mated females at each dose level. Maternal bodyweight gain was reduced at 450 and 900 mg/kg but only the latter was statistically significant. Mean foetal weights were significantly reduced in the 450 and 900 mg/kg bw groups. There was no evidence of teratogenicity at any dose level. The NOEL for foetoxicity was 100 mg/kg bw per day.

9. A test for gene mutation (HGPRT locus) in mammalian cells was performed. Butylscopolaminium bromide was tested both in the presence and absence of metabolic activation. Test substance concentrations studies ranged from 312.5 µg/ml to 5000 µg/ml (with and without S9). No cytotoxicity and no evidence of mutagenicity were present at any of the test concentrations, either in the presence or absence of S9. Human lymphocyte cultures were used in an *in vitro* clastogenic study, both in the presence and absence of metabolic activation. This study was conducted using two harvesting times of 24 hours and 48 hours. All concentrations of butylscopolaminium bromide tested (up to 5000 µg/ml), showed no evidence of chromosomal or chromatid damage in the two independent studies. Overall, there is no evidence of any mutagenic potential for this active ingredient.

10. No specific carcinogenicity studies were presented for butylscopolaminium bromide. Due to the fact that the compound contains an epoxide ring, an assessment was provided of the likely carcinogenic potential of this active ingredient. Based on the data presented, particularly with regard to mutagenicity, metabolism and model studies, it is considered unlikely that the epoxide ring in butylscopolaminium bromide would pose a significant carcinogenic risk.

11. Butylscopolaminium bromide had no microbiological activity. There was no evidence that it affected the immune system.

12. Butylscopolaminium bromide has been used for many years in human medicine as an antispasmodic agent which relaxes the smooth muscle of the organs of the abdominal and pelvic cavities. The oral dose is 10-20 mg 3-5 times daily; in acute spasm 20 mg, repeated if necessary after 30 minutes, may be administered by intramuscular or intravenous injection. The reported side-effects include dryness of the mouth, temporary loss of accommodation and tachycardia. It is contra-indicated in patients with glaucoma because of the mydriatic effect. No data was available on a pharmacological NOEL in humans.

13. A pharmacological NOEL for butylscopolaminium bromide in the dog, of 1 mg/kg bw, was available from an oral toxicity study, in which this dosage level was shown to be devoid of any effect on gastrointestinal tract motility. Using this NOEL value and applying a safety factor of 100, would lead to the establishment of an ADI in humans of 0.6 mg/person (0.01 mg/kg bw). This ADI is 50 times less than the minimum daily therapeutic dose in humans by the oral route.

14. In a pharmacokinetic study in the horse using radio-labelled butylscopolaminium bromide, concentrations of radioactivity in plasma fell rapidly from approximately 2 μg/ml 2 minutes after intravenous dosing to approximately 0.2 μg/ml 30 minutes after dosing. Residues were rapidly depleted from all tissues and were highest in the liver and kidney (14000 and 21000 μg/kg, respectively at 0.5 hours, 1100 and 200 μg/kg at 24 hours and 500 and 50 μg/kg at 48 hours), levels in muscle and fat were less than 30 μg/kg at 0.5 hours and less than 10 μg/kg by 48 hours. More than 50% of the administered dose was excreted in urine and more than 20% in faeces within 24 hours after administration and more than 20% was eliminated in faeces between 24 and 48 hours after administration. In total almost 45% of the dose was eliminated in faeces. 85% of the radioactivity in urine consisted of unmetabolised butylscopolaminiumbromide. Unmetabolised butylscopolaminium bromide was also the major component of the residues in liver and kidney.

15. Intravenous pharmacokinetic studies in pigs (0.1 mg butylscopolaminium bromide/kg bw) and cattle (0.2 mg butylscopolaminium bromide/kg bw) resulted in low plasma concentrations. In pigs plasma levels peaked at 0.79 μg/ml 0.5 hours after dosing and were less than 0.10 μg/ml from 4-48 hours after dosing. In cattle plasma levels did not exceed 0.11 μg/ml during the 48 hours after administration. In both species excretion was rapid with urinary concentrations peaking at 2-4 hours in cattle (around 10 μg/ml) and 4-8 hours in pigs (2.5 μg/ml). Urinary concentrations were less than 0.10 μg/ml after 24 hours for cattle and 32 hours for pigs.

16. Residue depletion was studied in the horse after a single intravenous administration (0.2 mg butylscopolaminium bromide/kg bw). Residues were below the limit of quantification (LOQ) (100 μg/kg) at the first slaughter time (6 days) in muscle, liver and kidney. In cattle given 0.3 mg butylscopolaminium bromide/kg bw intramuscularly, residues in liver, kidney, muscle and injection site were below 100 μg/kg by the first slaughter time (9 days). In pigs given a single intramuscular injection containing 0.5-1.3 butylscopolaminium bromide/kg bw, all samples of liver, kidney, muscle and injection site contained residues below 100 μg/kg by the first slaughter time (9 days). These studies measured residues of butylscopolaminium bromide using HPLC.

17. A further residue depletion study was performed in calves. 4 animals were sacrificed at each of 3 timepoints after 6 intramuscular injections of butylscopolaminium bromide (0.4 mg/kg bw at 12 hour intervals). At 24 hours post last dose, residue concentrations were below the limit of quantification (100 μg/kg) for muscle, kidney, liver and fat for all 4 animals. The mean injection site residue concentration was 140 μg/kg (range less than 100 to 250 μg/kg) at 24 hours post last dose and all samples were below the limit of quantification on days 18 and 28.

18. The residue depletion of butylscopolaminium bromide was studied in bovine milk also using HPLC. The study used only 3 animals given a single intramuscular dose of 0.25 mg butylscopolaminium bromide/kg bw. Samples were taken at intervals from 7 hours after treatment. Residue concentrations in all samples were below the limit of quantification (less than 0.10 mg/litre).

19. No residue depletion studies were provided regarding sheep and goats, however given the available data from another ruminant species (cattle) similar elimination is expected.

20. The proposed routine analytical method for the determination of residue was based on HPLC with UV detection. The limits of detection and quantification were reported to be 0.05 and 0.10 mg/kg for the liver, kidney and muscle of the bovine, porcine and horse. The same limits of quantification and detection were also quoted for residues in urine and plasma and also for bovine milk. Extensive clean-up procedures were required for kidney, liver and muscle and recovery values for these tissues were very poor. The analytical method was specific for butylscopolaminium bromide and there was no interference from the matrix elements, from metamizole metabolites, nor from "apo-Buscopan".

Conclusions and recommendation

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

- the substance is used in individual animals on an infrequent basis,
- in all species, including humans, it is poorly absorbed from the gastro-intestinal tract,
- residues in tissues and milk are rapidly depleted in cattle, information on other species demonstrates a similar pattern;

the Committee considers that there is no need to establish MRLs for butylscopolaminium bromide 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
Butylscopolaminium bromide	All food producing species	