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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

NEOSTIGMINE

SUMMARY REPORT

1. Neostigmine is a quaternary ammonium compound of the group of carbamates and is used for the treatment of gastrointestinal stasis, myasthenia gravis and as an antidote to curare in animals.

   Neostigmine bromide is administered by subcutaneous injection at a dose of 25-50 µg/kg bw, and is indicated for all mammalian species.

2. Neostigmine is used in human medicine for the treatment of myasthenia gravis, the management of paralytic ileus and to combat the non-depolarising neuromuscular block induced by the muscle relaxants used in anaesthesia.

3. Neostigmine inhibits cholinesterase activity, prolonging and intensifying the physiological actions of acetylcholine. Neostigmine possesses a carbamyl ester linkage that is hydrolysed by acetylcholinesterase, but at a much slower rate than is acetylcholine itself. The duration of inhibition of acetylcholinesterase by this carbamylating agent is approximately 4 hours in man. Neostigmine potentiates both the nicotinic and muscarinic effects of naturally occurring acetylcholine. Furthermore, it may have direct effects on acetylcholine receptors in skeletal muscle. Neostigmine can inhibit the muscle relaxant effects of curare-like drugs in many species.

4. In rats the LD_{50} is 51mg/kg bw after oral administration and 165 µg/kg bw after intravenous administration. In mice, the LD_{50} after oral administration is 7 mg/kg bw and after intravenous administration is 160 µg/kg bw.

5. Adverse reactions to neostigmine relate to excessive cholinergic stimulation. No specific mutagenicity or carcinogenicity studies have been performed with neostigmine. No link between exposure to neostigmine during human pregnancy and congenital malformations has been reported.

6. No other information on the toxicity of neostigmine is available except that it is a quaternary ammonium compound.

7. Neostigmine bromide is poorly absorbed from the gastro-intestinal tract. The actual absorption mechanism for neostigmine bromide has not been determined, but animal studies suggest that it is absorbed intact and that no hydrolysis takes place in the intestinal wall. Following oral dosing in humans, 20% of the dose is excreted in urine, with 5% as unchanged drug. Approximately 50% of the dose is excreted in faeces. Peak plasma concentrations following a 30 mg oral dose of neostigmine in man vary between 1 and 5 µg/l. Overall, the oral absorption of neostigmine bromide in man is reported to be less than 40% of the administered dose.

8. Neostigmine is extensively hydrolysed by plasma esterases and the quaternary alcohol and parent compound are excreted in the urine; the half life of neostigmine is only 1-2 hours in man.

   Experimental studies in rats and in man show that the main metabolite of neostigmine is 3-hydroxyphenyltrimethyl ammonium. This compound, and other unidentified metabolites account for 30% of urinary excretion in the first 24 hours post oral dosing in man. In rats the metabolite is conjugated and excreted in the urine as the glucuronide.

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9. No information is available on residue depletion in target animals.

The normal recommended therapeutic dose in animals is 25-50 µg/kg, giving rise to a total subcutaneously injected dose of 12.5-25 mg neostigmine bromide for a 500 kg animal. Even in the worst case scenario, where this entire site was ingested immediately following injection, this level of exposure would have to be compared with the recommended adult therapeutic dose in humans of approximately 15-90 mg daily (in divided doses) for the treatment of myasthenia gravis.

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 :

- neostigmine is used in a small number of individual animals for infrequent or non-regular treatment,
- is poorly absorbed from the gastro-intestinal tract,
- is rapidly metabolised and excreted;

the Committee considers that there is no need to establish an MRL for neostigmine 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
Neostigmine	All food producing species	