The European Agency for the Evaluation of Medicinal Products

oEMEA/MRL/054/95-FIINAL
February 1996

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CARBETOCIN

SUMMARY REPORT

1. Carbetocin (CAS-name: 1-butanoic acid-2-(O-methyl-L-tyrosine)-1-carbaoxytocin), a cyclic oligopeptide, is a synthetic strucural analogue to oxytocin with the following changes in the molecule: replacement of the amino-group of cystein (position 1) by a hydrogen atom, of its disulphide bond by a thioether bond, and of the hydroxyl group of tyrosin (position 2) by a methyloxylgroup.

2. In veterinary medicine carbetocin is used following subcutaneous or intramuscular injection for:

   - Stimulation of uterine contractions to facilitate partutition, promotion of involution of post parturient uterus, expulsion of pathological uterine contents (e.g. placental retention, incomplete abortion) in cattle, pigs, sheep and goats,
   - Promotion of milk let-down in cases of agalactia and supporting therapy in the pig MMA-syndrome, initation of the milk ejection reflex in cattle, pigs, sheep and goats,
   - Following $PGF_{2\alpha}$ pre-treatment: synchronisation of parturition in pigs.

   The recommended doses range from 0.035-0.07 mg/animal (sheep, goats) to 0.1-0.2 mg/pig and 0.175-0.35 mg/cow. The action of 1 mg Carbetocin is comparable to that of 50 IU oxytocin, corresponding to 0.084 mg of the synthetic oxytocin standard.

3. Carbetocin, like oxytocin, exerts its main action on the smooth muscle fibres of the female reproductive organs (induction and increase of contractions). Binding to specific receptors of the muscle cells stimulates calcium influx and inhibits ATP-dependent calcium efflux improving contractility. In the estrogen stimulated uterus irregular and weak contractions become regular and forceful, in the lactating mamma milk ejection results. In food producing animals the carbetocin-induced motility resembles more to physiological labour than results of exogenous oxytocin. Carbetocin stimulates uterine contractions threefold longer and with a 25% higher increase in frequency than exogenous oxytocin. The duration of its action thirty-fourtyfold longer. Its increased potency is explained by delayed metabolism and prolonged receptor interaction.

4. Absorption from the injection site in cattle and pigs is rapid and results in pharmacological effects after 3 min. Plasma concentrations in cows return to baseline values within 24 h. Carbetocin is metabolised like oxytocin by enzymatic break down. The metabolic pathway reported for oxytocin is inactivation by reduction of the disulfide bond in kidney, liver, or lactating mamma follwowed by mainly renal excretion (30-35% of the total radioactivity after administration of tritiumlabelled oxytocin >1% immunoreactive oxytocin). A similar excretion must be assumed for carbetocin, as the structural changes result in higher protease and disulphidase stability but only retard metabolism. The assumption is supported by the fact that 24 h after subcutaneous application of tritiumlabelled carbetocin the highest amounts of radioactivity (not quantified) were recovered from kidneys while liver contained half of that amount. Metabolites of carbetocin have not been identified. Plasma half-lives of carbetocin are biphasic with a $t_{½\alpha}$ of 7.5-10 min and a $t_{½\beta}$ of 85-100 min in pigs. The reported plasma half-lives for oxytocin are a $t_{½\alpha}$ of 1-9 min and a $t_{½\beta}$ of 22-26 min. As oxytocin, orally administered

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carbetocin will be degraded by gastrointestinal tract enzymes into inactive smaller peptides and amino acids.

5. In humans the intramuscular bioavailability of carbetocin reaches ca. 80%. Of a therapeutic dose up to 6% are excreted in milk with maxima at 120-240 min post administration. For carbetocin a half-life for the elimination phase ($t_{½ß}$) of 40 min and a renal clearence of maximal 0.7% are observed in non-pregnant volunteers. Carbetocin, like oxytocin, induces tetanic contractions of the human uterus when given intramuscularly 24-48 h post partum, though of approximately fourfold longer duration.

6. The subcutaneous and intravenous LD_{50} of carbetocin in rats are >10 mg/kg bw (therapeutic dose in cows: 0.35 mg/cow). Oral administration of 1 mg carbetocin/rat for 15 days caused deviations of haematological parameters within normal limits and enlargement of spleen and kidneys. Testing tolerance at the injections site in chinchilla rabbits receiving carbetocin or physiological saline similar histological reactions were seen in all animals. Carbetocin was reported not to be mutagenic in a Salmonella/microsome assay with and without metabolic activation.

7. No NOEL which could serve as base for the establishment of an ADI can be identified for carbetocin. However, carbetocin is very similar to oxytocin in structure and activity.

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:

- after oral administration carbetocin is degraded to inactive smaller peptides and amino acids by gastrointestinal tract enzymes,
- carbetocin is rapidly absorbed from the injection site and rapidly excreted and metabolized,
- carbetocin is used once or with one repetition during a well defined, limited period of time.

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

Pharmacologically active substance(s)	Animal Species	Other Provisions
Carbetocin	All mammalian food producing species	