COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

OXYTOCIN

SUMMARY REPORT

1. Oxytocin is a naturally occurring hormone present in the female and male organism of all mammalian species. Its chemical structure is a nonapeptide. Endogenous Oxytocin is produced in the nucleus supraopticus and the nucleus paraventricularis of the hypothalamus. By neurosecretion the hormone migrates to the posterior lobe of the hypophysis where it is stored. It is released in response to nervous stimuli. Synthetic oxytocin is structurally identical to the naturally occurring hormone.

   Oxytocin and its synthetic analogue have been used for a long time in human and veterinary medicine. Various published literature is available and the applicant refers to these sources and justifies the fact of not submitting new studies by the existence of sufficient data in literature.

2. The indications claimed for in veterinary medicine are: stimulation of uterine contractions to facilitate parturition, promotion of involution of post parturient uterus, retentio secundinarium, control of post partum hemorrhage and promotion of milk let-down in cases of agalactia. The target species concerned are cattle, horses, pigs, sheep and goats.

   The proposed doses for subcutaneous or intramuscular administration of oxytocin are 10-50 IU for cattle, 5-50 IU for horses, and 5-30 IU for pigs, sheep and goats. For intravenous administration one quarter of these doses is recommended.

3. For the description of pharmacodynamic effects the applicant solely refers to standard text books on reproductive physiology and pharmacology. Oxytocin exerts its main physiological and pharmacological effects on the smooth muscle fibers of the female reproductive organs (induction and increase of contractions). Oxytocin changes the weak spontaneous and irregular contractions of the estrogen stimulated uterus into regular forceful and purposeful contractions. On the lactating mamma oxytocin provokes contractions of the myoepithelial tissue thus causing milk-ejection and at suckling stimulus milk- let-down. Oxytocin influences at physiological levels diuresis and saluresis. Effects on vascular muscles (constriction or dilatation) are various and depending on type of vessel, species, hormonal dominance of estrogen, gestagen and dose administered.

4. A study on pharmacokinetics was performed with the commercial product Intertocine-S in ovariectomised goats and goats in anoestrus (2 animals/group). Each animal received a single intravenous injection of 2 µg oxytocin/kg bw, corresponding to approximately 50 IU/ animal. A rapid initial distribution phase and a slow elimination phase were observed with mean t+values of 1.94 min and 22.3 min, respectively. Further pharmacokinetic studies were not performed as data from literature demonstrate that half life of oxytocin is very short.

   According to published literature oxytocin is inactivated by reduction of the disulfid-chain in the kidneys, the liver or the lactating mamma and eliminated mainly by renal excretion (35-50 % intact oxytocin and a glycinamid as inactivated metabolite). Biphasical elimination processes are described with an initial t+ of 1-9 min (in dependence on species studied) followed by a slower process with t+ of 22-26 min.

5. The applicant did not submit data on the toxicity of oxytocin. From the literature it is known that acute toxicity of oxytocin is low (intravenous LD_{50} in rat 5.8 mg/kg).

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6. There are no data on mutagenicity, cancerogenicity and teratogenicity but oxytocin does not belong to any of the substance groups for which carcinogenic or teratogenic properties have been assumed or proven.

7. Reproductive studies were not performed because, as the applicant argues, the product will be used only during very late pregnancy or after parturition, a period when endogenous oxytocin is secreted as well.

8. According to literature adverse effects have only been noted with high doses of oxytocin given for a long period of time (several oestrus cycles). In cows a decrease of the oestrus cycle length and morphological changes of the mucosa of the reproductive tract have been observed. In hamsters the duration of pregnancy was reduced. However these effects are not relevant for the safety evaluation as the indicated use of oxytocin is only for a short period of time and not in such high doses.

9. After oral administration oxytocin as a nonapeptide is degraded into inactive smaller peptides and amino acids by enzymes of the gastrointestinal tract. In order to demonstrate oral inactivity of oxytocin the applicant performed a study in cocks. Five cocks were injected single intravenous doses in a range of 0.04-0.08 IU oxytocin or received an intragastric administration of 4-8 IU oxytocin. While intravenous treatment caused a decrease in blood pressure of 60-120 mm Hg, intragastric treatment did not produce any effect.

10. Residue depletion studies and a routine analytical method were not provided.

11. A clear NOEL which could serve as base for the establishment of an ADI was not established. However, with regard to the chemical and biological characteristics identical to endogenous oxytocin, its oral inactivity and its intended clinical indications with single or only few applications during a well defined limited period of time, the substance is considered a candidate for Annex II of Council Regulation (EEC) Nº 2377/90 for all mammalian species.