COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ROMIFIDINE

SUMMARY REPORT

SAFETY FILE

1. Romifidine is a member of the chemical class of the imino-imidazolines. It is structurally and pharmacologically closely related to Clonidine, a compound used in human medicine as an anti-hypertensive drug. In veterinary medicine, Romifidine is administered intravenously and indicated for sedation and preanesthetic medication of horses.

2. Extended investigations were performed on the pharmacological and toxicological properties of Romifidine. Most of the studies presented were conducted according to GLP or other adequate standards. Receptor binding studies revealed that Romifidine exerts high affinity to alpha 2-adrenoceptors and to a lesser extent also to alpha 1-adrenoceptors. The physicochemical properties, mechanism of action, and the spectrum of effects produced equalled those of the structurally related Clonidine.

   Romifidine was studied in various laboratory animal species, following oral or parenteral administration and was shown to affect several functional systems via a central and/or peripheral site of action. The most relevant effects are lowering of blood pressure and heart rate, alterations of the sleeping/waking state, sedation and slight analgesia. Also mydriasis, contraction of the nictitating membrane (cat), reduced lacrimal flow, inhibition of the secretion of gastric juice and acid, prolonged intestinal transit time, increase (rat) or decrease (dog) in excretion of urine, and hypoglycaemia (rat) were observed. A pharmacological NOEL of 0.005 mg/kg bw was derived from EEG- tracings in rabbits.

   Following oral application, the predominating metabolite of Romifidine in the target animal horse, compound STH 2337, exerted no effects in EEG tracings in rabbits, nor did it affect the nocturnal motility of mice. No changes of the blood pressure and heart rate were observed after intravenous administration to rabbits.

3. The pharmacokinetic properties of Romifidine showed a high degree of consistency in rats, dogs, and horses following intravenous or oral administration. Plasma half lives were 1.5 and 2 hours in rats and dogs, respectively. In horses, the degradation of Romifidine following intravenous injection occurred too rapidly for observation. The extended serum half life of total radioactivity of 37 hours observed in horses treated with 14-C-Romifidine was therefore attributed to the occurrence of metabolites.

   The oral absorption was found to be almost 100% in rats and dogs. Due to rapid degradation the bioavailability of the unchanged parent compound accounted for only 35% in dogs.

   Following i.v. administration of radiolabelled Romifidine, about 80% of total radioactivity are eliminated via the kidneys, while only small amounts (12% in rats, 8% in dogs) were excreted with the feces. The existence of an enterohepatic circulation was suggested for rats and dogs.

4. Romifidine metabolites were isolated from 24 hour urine samples from rats and from 5 day pooled urine samples from dogs. In horses, metabolite profiling was performed in edible tissues 3 and 24 hours after treatment and in 24 hour urine samples.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel: (+44-171) 418 84 00 Fax: (+44-171) 418 84 16

Metabolic pathways proposed for dogs and horses were in close agreement and it was suggested that Romifidine is degraded by cleavage at the imidazoline ring leading to a metabolite designated as STH 2324 or the corresponding hydroxylated product ESR 1235 via the intermediary products STH 2401, STH 2336 and STH 2337. ESR 1235 was also suggested to be generated via hydroxylation of the parent compound (leading to ESR 1231) and this route was assumed to be favoured in male horses. The evidence of sex differences in horses, however, was not confirmed due to the limited number of animals used.

Residues found in liver and kidney from horses included unchanged parent compound and STH 2337 (the main hepatic metabolite), ESR 1235, STH 2324 and STH 2401. In muscle tissue, parent compound and STH 2324 were detected.

No detailed metabolic pathway was proposed for rats but a high degree of consistency with the principal degradation steps in dogs and horses can be assumed. There are evidences suggesting that the metabolites STH 2337 and STH 2324 found in horses correspond to metabolites STH 2336 and M III identified in rats. Metabolite ESR 1235 from horses was not identified in rats. About 10 % of the urinary metabolites were not identified.

5. LD-50 values were determined in rats, mice, rabbits and dogs and were in the same order of magnitude in respect to the mode of administration (LD-50 i.v.: 30 - 60 mg/kg bw, LD-50 oral: 175 - 255 mg/kg bw, LD-50 s.c. (mouse):110 mg/kg bw). Symptoms seen with high doses of Romifidine comprised tremor, ataxia, ruffled fur, exophthalmus, mydriasis and clonic/tonic convulsions. In dogs, no oral LD-50 value was established due to emesis occurring after administration of the substance.

6. No NOEL's were established from repeated oral dose toxicity studies of 13 weeks duration performed in rats and dogs, since effects occurred even at the lowest doses tested (0.15 mg/kg in rats, 0.03 mg/kg bw in dogs). Many effects seen at the low dose levels corresponded to the pharmacological properties of Romifidine, comprising reduced activity, slight sedation, reduced food intake with decreased body weight gain and reduction of plasma protein, lowered blood pressure and heart rate. At higher doses, reduction in erythrocyte count, haemoglobin concentration and haematocrit as well as increased liver enzyme levels and hyaline deposits in hepatocytes in dogs (0.3 mg/kg bw) and deposition of haemosiderin in rat lungs (0.4 mg/kg bw) were observed as clear toxic effects.

   The etiology of reduced red cell parameters was not explained. Values were only slightly below the normal range and had completely reversed in recovery animals. Elevation of liver enzymes and hepatocytic hyaline deposits were suggested to result from cytolysis produced by the Romifidine related initial blood pressure raise and a possible subsequent elevation of intrasinusoidal liver pressure.

7. Three tolerance studies in the target animal horse were presented. Romifidine induced dose dependent sedation and analgesia after oral and parenteral administration with appropriate sedation achieved at 0.1 mg/kg bw.

   Romifidine also produced cardiovascular depression indicated by bradycardia, prolongation of the atrioventricular conduction time and lowered blood pressure. Perspiration, prolapse of the nictitating membrane and the penis, oedema of the head and the lower abdomen, flatulence and increased urinary excretion were also observed. Haematological effects (decreased haemoglobin and haematocrit, elevated leucocyte counts and increased blood glucose) were noted.

8. Effects of Romifidine on the reproductive performance were investigated only in segment II studies (embryotoxicity/ teratogenicity) in rats and rabbits. The design of the rat study exceeded common requirements , since some of the pups (F1) were raised up to adulthood and produced a F2- generation.

   A NOEL was not derived since reduced food intake and body weight gains in the parent rats and lowered fetal weights occurred even at the lowest dose (0.15 mg/kg bw, oral). These effects were explained by the drug related inhibition of gastric secretion with malnutrition of dams as consequence.

Rabbits appeared less susceptible and no effects in dams and their offspring were observed at oral doses of 0.15 and 0.4 mg/kg bw. It was concluded that Romifidine induced embryotoxic effects occur only at oral doses higher than 0.15 mg/kg bw in rats and at oral doses higher than 1 mg/kg bw in rabbits. The observed slight retardations in fetal development may be partly attributed to the drug related sedative effects on the parent generations.

Additional segment II studies with related compounds (St 600 Cl, St 567 Br, St 91 Cl, Clonidine) revealed embryotoxic effects (elevated resorption counts, reduced fetal birth weights) only at high doses, which were paralleled by marked toxic symptoms in dams. Teratogenic effects were not seen in any case. When tested at similar doses, comparable effects were seen with Romifidine and Clonidine.

No specific segment I (fertility, embryotoxicity, teratogenicity) and segment III (peri-, postnatal- period) studies were performed with Romifidine. In place of this segment I and segment III studies with the Romifidine related compounds Clonidine, St 600 Cl, St 567 Br, and St 91 Cl were presented.

In a segment I study with Clonidine, reduced weight gain in parent rats and increased preimplantation losses and resorptions and elevated incidence of deaths among pups were seen at 0.015 and 0.15 mg/kg bw.

These results were not confirmed in two additional experiments in which doses of 0.015 and 0.075 mg/kg bw were without effect. Borderline effects on the implantation rate and mean birth weight of fetuses noted in one study were not confirmed in the second trial. As reported in a submitted summary report on additional studies in mice, Clonidine produced embryotoxic effects at an oral dose of 2 mg/kg bw but not at lower doses.

Study results obtained with St 600 Cl, St 567 Br, and St 91 Cl in rats were also negative. NOELs were derived for each substance and ranged from 1 to 12 mg/kg bw.

In a segment III study with Clonidine in rats toxic effects such as exophthalmus, piloerection and reduced weight gain in dams and decreased weight gain and slowed development as so called "borderline effects" in their young occurred at 0.15 mg/kg bw. No effects attributable to treatment were seen at 0.015 or 0.075 mg/kg bw.

No teratogenic effects were seen in any of the studies presented.

9. The results of a complete battery of mutagenicity tests with Romifidine (Ames test, HPRT test, micronucleus test in mice) and of numerous mutagenicity studies with different endpoints with Romifidine related substances (Clonidine, St 567 Br, St 600 Cl, STH 2148 Br) were considered negative.

10. The carcinogenic potential of Romifidine was not specifically evaluated. Instead, the applicant provided two long-term feeding studies in mice (78 weeks) and rats (132 weeks) with Clonidine.

    Mice treated with Clonidine at dose levels of 1.1 or 2.5 mg/kg bw/day showed reduced body weight gains. All treated mice exhibited an increased incidence of islet cell hyperplasia in the pancreas which was attributed to the observed hyperglycemic action of the compound rather than to a toxic effect. Neoplastic changes detected in treated mice did not differ from those observed in control animals.

    In the rat study, Clonidine was administered via the feed at concentrations of 5, 10 or 20 mg/kg. Additional groups received the anti-sympathotonic acting substance Reserpine or a combination of both Clonidine and Reserpine.

    A variety of adverse effects such as aggressiveness, irritancy, piloerection, ataxia, bloody noses and eyelids were observed in all treatment groups. During the first weeks of treatment, Clonidine or Reserpine as well as the combination of both drugs caused a reduction in body weight gain and increased mortality mainly in the high dose groups. Clonidine did not exert a tumorigenic effect. The strength of the results was limited by marked toxic effects in rats of the high dose group resulting in decreased body weight gain and vitality.

11. No studies on the immunologic properties of Romifidine were presented.

    Romifidine was not tested for skin sensitising potential.

12. When Romifidine was administered orally to healthy male volunteers, slight sedation and a reduction of blood pressure were observed at doses of 0.2 mg/person (approx. 0.003 mg/kg bw) or 0.3 mg/person (approx. 0.005 mg/kg bw) compared to placebo treated individuals. One person treated with 0.075 mg (approx. 0.001 mg/kg bw) showed similar symptoms.

13. An ADI of 0 - 3 µg/person based on the pharmacological NOEL of 0.005 mg Romifidine/kg bw derived from EEG tracings monitored in an oral rabbit study and applying a safety factor of 100 was established (60 kg x 5 µg/kg bw/100). A clear NOEL based on human data could not be derived but the established ADI ensures a sufficient margin of safety. Metabolite STH 2337 can be calculated to contribute to a maximum of 3% to the pharmacological activity of the total residue in horses and is regarded as irrelevant with regard to consumer safety.

RESIDUE FILE

1. The metabolic profile of Romifidine was investigated in liver, kidney and muscle from the horse at early timepoints post dose (3h and 24h). The composition of the residues in fat was not investigated. The parent compound was the major component in muscle and kidney (about 60% of the extractable radioactivity), but only a minor component in liver (about 4%). The metabolite STH 2337 was the major component in liver (41 - 51% of the extractable radioactivity, 3 h post dose) and the minor component in kidney (9% - 10%). No information is available on the metabolic profiles in the target tissues at timepoints later than 24h.

2. Residue depletion was studied in horses following i.v. treatment with 14C-Romifidine in the projected commercial formulation at dose levels of 0.093 - 0.127 mg/kg bw. Total residues were highest in liver and kidney. Depletion was more rapid in kidney than in liver. At 3 days after treatment, the total residue concentrations in muscle and fat were below the limit of determination of 1 µg/kg. At 5 days after treatment, the sum of residues in 100 g liver and 50 g kidney was still above the ADI of 3.0 µg.

3. A 3H-radioimmunoassay was developed and validated for the determination Romifidine in horse liver, kidney, muscle and fat. Precision and accuracy were satisfactory. The limit of detection was 0.2 µg/kg. The limits of quantitation were about 1 µg/kg for liver and 5 µg/kg for kidney, muscle and fat. The antiserum shows specificity for Romifidine and the structural-analogon Clonidine (STH 155), but not for the metabolites of Romifidine.

   For the reasons stated below, it is recommended that a maximum residue limit is not required and the compound be entered into Annex II for target species ´equidae`:

   - Romifidine is intended for use as a sedative and as preanesthetic medication in individual horses. Mass treatment of horses is not an indication of this compound;
   - the clinical indication of Romifidine renders its use in horses bound to be slaughtered soon very unlikely.
   - Only residues with pharmacological activity have to be considered.

   However, the total residue of Romifidine contained in the standard food package exceeds the established ADI of 3 µg/person for several days. Therefore, the setting of a withdrawal period of appropriate length should be considered.