



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

OMEPRAZOLE

SUMMARY REPORT

1. Omeprazole (R,S)-5-methoxy-2-[[[(4-methoxy-3,5-dimethylpyridine-2-yl)methyl]sulphonyl]-1H-benzimidazole (CAS Number 73590-58-6) is a substituted benzimidazole which inhibits gastric secretion in animals and humans. It is intended for use for treatment of gastric ulcers in horses as an oral paste containing 37% w/w omeprazole at the dose of 4 mg omeprazole/kg bw/day for 28 days, followed by an additional treatment period of 30 days at a dose of 2 mg omeprazole/kg bw/day to prevent recurrence.

In humans omeprazole has been widely used since the 1980's to reduce gastric secretion as an aid in the treatment of for instance peptic ulcers.

2. Omeprazole exerts its pharmacodynamic activity via an interaction of the H⁺/K⁺-ATPase the gastric proton pump-in the secretory membrane of the parietal cell. Activated H⁺/K⁺-ATPase enzymes are inhibited intracellularly, thus leading to a transitory inhibition of the gastric acid production of the cell. After oral administration omeprazole is absorbed from the small intestine and carried by the blood to the parietal cell of the stomach. Here it rapidly reacts with activated H⁺/K⁺-ATPases to form a disulphide enzyme inhibitor complex. When a sufficient number of enzymes are inhibited, the acid secretion of the cell will decrease and the pH of the stomach content will raise. This pH increase will eventually lead to an increase in the release of gastrin and thereby an effect on the gastrin-dependent parameters in the stomach. The metabolites of omeprazole were tested for pharmacological effect directly on the H⁺/K⁺-ATPase and in isolated rabbit gastric glands. Although some metabolites showed *in vitro* activity against the isolated enzymes, the inhibitory effect of the metabolites on the gastric acid secretion of the cells are very much lower than the parent compound.
3. The pharmacokinetics of omeprazole was studied in rats, mice, dogs, horses and humans. The compound is acid labile, and omeprazole has only 15% bioavailability after oral administration in the dog compared to 70% bioavailability after intraduodenal administration. Maximum plasma levels are obtained 45 minutes after oral administration in the dog and 10 minutes after oral administration in the mouse. The half-life of omeprazole is very short with a t_{1/2} of 5 to 9 minutes in the mouse, 1 to 1.3 hours in the dog and 1.5 hours in humans. Protein binding of omeprazole is 85 to 95% in rats, dogs and humans. After intravenous or oral administration to rats the highest concentrations of radiolabelled compounds were found in liver, kidneys, duodenum and stomach and lowest concentration were found in brain and fat, after 0.5 hour.

Metabolism after intravenous and oral administration is extensive in rats, mice and dogs with only trace amounts of the parent compound found in urine. After oral administration to rats and dogs 90 to 100% of the radioactivity from ¹⁴C-labelled omeprazole is excreted within 72 hours with 20 to 30% recovered in urine and the remainder in faeces.

The metabolic pattern seems to be qualitatively similar between species (dogs, rats and mice) and the variations observed were mainly quantitative. Seven major metabolites which accounted for about 50% of the excreted amount in the rat and 70% in the dog were chemically described. The major metabolic pathway in the dog is *via* aromatic hydroxylation and glucuronide formation, while in the rat aliphatic hydroxylation and subsequent oxidation is more prominent. In mice, the two major metabolites, a sulfone of omeprazole and a sulfide of omeprazole, reached their maximum within 30 minutes with peak concentrations of 25 to 67% and 2 to 9% of omeprazole, respectively. The half-life of the omeprazole sulfone compound was about 10 minutes whereas the half-life of the omeprazole sulfide compound was longer with a terminal half-life of more than 2 hours. No accumulation was found after 7 days of treatment in rats and humans and no change in the pharmacokinetic disposition of omeprazole after 7 years of daily treatment in dogs.

In horses, omeprazole was administered 3.0 to 3.4 mg/kg bw in an oral paste, the bioavailability of the oral paste was calculated to be 10.5%. In gastric cannulated horses, the gastric acid suppression and the plasma omeprazole levels were evaluated after an oral dose of 4 and 5 mg/kg bw administered in paste. The C_{max} was 385 to 693 $\mu\text{g/l}$ (average 548 $\mu\text{g/l}$) after the 4 mg/kg bw dose treatment.

In a radiolabelled study using an oral dose of 1 mg/kg, the C_{max} for omeprazole was 137 $\mu\text{g/l}$, which is 25% of the value found in the 4 mg/kg bw study. The plasma concentrations of omeprazole were below the limit of quantification (0.0086 mg/l) from 2 to 4 hours after treatment. The radiolabelled study also evaluated intravenous administration of 0.5 mg/kg bw. Metabolism after intravenous and oral administration is extensive also in horses with only trace amounts of the parent compound found in urine. 43% to 61% of the administered radioactivity was excreted in urine and the remainder in the faeces. The two major metabolites in urine were the glucuronides of H182/68 and hydroxylated omeprazole sulphide formed *via* O-demethylation or hydroxylation of the parent compound, and 4 of the minor metabolites were identified. In liver and muscle 1 hour after treatment the major residues were reduced omeprazole and a methyl sulphide metabolite.

The following pharmacokinetic parameters were found for total radioactivity (omeprazole and metabolites) after intravenous administration of 0.5 mg/kg bw to horses: the elimination half-life ($t_{1/2}$ elimination) was 1.3 to 3.45 hours, clearance was 5 to 6 ml/min/kg, and the volume of distribution (Vd) was 0.6 to 1.8 l/kg. The area under the concentration-time curve (AUC) was on average 1.5 mg equivalent.h/l. For total radioactivity (omeprazole and metabolites) after oral administration of 1.0 mg/kg a peak was observed one hour post dose (C_{max} = 0.5 to 1.3 $\mu\text{g/ml}$ equivalent). Thereafter radioactivity declined with a $t_{1/2}$ of 2.6 to 10.0 hours. Clearance rate was in the range 5.4 to 8.4 ml/min/kg, Vd was 1.2 to 6.35 l/kg. AUC was close to 2 μg equivalent.h/ml. Radioactivity was at or below the limit of detection at 24 hours after treatment. Based on comparison of C_{max} values, repeated administration did not result in accumulation.

4. Acute toxicity was investigated in rats and mice of both sexes after oral dosage. The acute oral LD_{50} was 1520 mg/kg for male mice and 1480 mg/kg on day 1 and 1380 mg/kg on day 14 for female mice. The acute oral LD_{50} was less than 5010 mg/kg for male rats and 3610 mg/kg on day 1 and 3320 mg/kg on day 14 for female rats. All deaths occurred within 1 to 2 days, and most of the surviving animals were free of symptoms within 24 hours. Signs of toxicity were reduced activity, reduced temperature and respiration, twitching and tremor.

No intravenous LD_{50} could be calculated due to very few deaths, since the low solubility of the compound was a limiting factor in the intravenous administration.

5. In a 3-month repeated dose toxicity study in rats, five groups with 10 males and 10 females per group, were dosed orally with 0, 13.8, 43.1, 138 or 414 mg/kg bw/day. There was a tendency to increased hyperkeratosis of the squamous epithelium in the transitional zone between the fore-stomach and glandular mucosa observed in the high dose group, which could indicate a low-degree of chronic gastric irritation. An increase in liver and kidney weights seemed to be a physiological adjustment to the drug elimination without histological signs of toxic effects. A toxicological NOEL of 43.1 mg/kg bw/day was retained, based on organ weights, microscopic pathology, clinical chemistry and hormone analyses.

In a 3-month repeated dose toxicity study in dogs, five groups with 2 males and 2 females per group were dosed orally with omeprazole in Methocel solution once daily with 0, 1.035, 5.5, 27.6 or 138 mg/kg bw/day. A slight decrease in packed cell volume (PCV), serum proteins and triiodothyronine (T3) was observed mainly in the high dose group. Slight atrophic changes in the gastric mucosa were found in the 3 highest dose groups. No other treatment related changes were found. The toxicological NOEL was 1.035 mg/kg bw/day in this study.

In another 3-month repeated dose toxicity study in dogs, two groups of dogs with 2 males and 2 females in each group were dosed orally, once daily, with 138 mg/kg bw/day. A similar control group received placebo. One treated group and the control group were sacrificed after the treatment period while the remaining group was sacrificed after 3 additional months without treatment. Autopsy showed similar atrophic gastric mucosa as seen previously immediately after termination of the 3 months of treatment. The dogs that were left to recover for three months after the end of treatment showed complete recovery of the chief cell changes, but a discrete focal fibrosis in the lamina propria and the induced hypertrophic foldings of the fundic mucosa persisted.

6. Three 2-year toxicological studies in rats and a 1-year and a 7-year study in dogs were carried out with special emphasis on the carcinogenicity.

In the three 2-year studies in rats using oral doses of 0, 1.7, 3.4, 13.8, 14.1, 44.0 and 140.8 mg/kg bw/day clinical and pathological changes observed after treatment with omeprazole were investigated. A dose-related increase in stomach weight and mucosa thickness was observed, strictly related to the gastrin concentration, corresponding to the known trophic effect of gastrin on the stomach. A time- and dose-related increase in both the incidence and the degree of severity of the Entero-Chromatofin-Like (ECL) cell hyperplasia including ECL-micronodules was observed. No long-term toxicological NOEL in rats could be established from these studies as effects were observed at all doses.

In the 1-year study in dogs given daily oral doses of 0, 0.7, 5.5 or 28 mg/kg bw/day, the only pathological changes occurred in the acid-secreting areas of the gastric mucosa of the 5.5 and 28 mg/kg bw/day groups. The changes consisted of a reversible atrophy of the chief cells in the dogs receiving 28 mg/kg bw and a rugal hypertrophy at doses of 5.5 mg/kg bw/day and above, which was not alleviated after 4 months. Both findings are believed to be linked to the acid inhibitory effect of omeprazole. No changes were found in the lowest dose group and therefore the toxicological NOEL was 0.7 mg/kg bw/day.

In the 7-year study in dogs it was shown, with daily doses of 0 or 0.17 mg/kg bw/day, that the disposition of omeprazole, as expressed by the area under the AUC, was not affected by repeated dosing. Neither basal nor meal stimulated gastrin levels showed any statistically significant difference between the control and omeprazole treated groups. The mean inhibition of acid secretion in the omeprazole treated animals was about 50%. There was no trend of change over time during the 7 years of treatment. There were no clinical, paraclinical or pathological changes related to treatment.

7. Tolerance in target species were evaluated in 4 studies.

Thoroughbred and standardbred adult horses were administered omeprazole paste at 5 times the recommended dose for 91 days. In another study 10 times the recommended dose was administered for 21 days. There were no treatment related adverse effects, as measured by clinical chemistry, haematology, physical examination and macroscopic or microscopic evaluation at necropsy. Minor variations of some serological parameters were observed but they were all considered to be without clinical significance.

In breeding stallions, administration of omeprazole paste at 3 times the recommended dose for 71 days had no effects on reproductive parameters or on behaviour.

In foals administration of omeprazole paste at 3 times and 5 times the recommended dose for 91 days resulted in increased stomach-weight/bodyweight ratio, but there were no histopathological changes in the mucosal thickness or enterochromafin-like cells.

8. Effects on reproduction were evaluated in a study in rats administered 0, 13.8, 43.1 or 138 mg/kg bw/day orally. Treatment was from 2 weeks pre-mating to 3 weeks post partum for the females and from 9 weeks pre-mating to 3 weeks post mating for the males. Half of the females in each group were sacrificed on day 21 of pregnancy, examined for reproductive performance and subjected to a pathological examination. The remaining dams and litters were sacrificed and examined at day 21 post partum. The only effects were slight, non-significant decreases in litter size, viability and growth in the 138 mg/kg bw group. The NOEL for reproductive toxicity was 43.1 mg/kg bw/day in rats. No 2-generation study was provided.

9. The potential for teratogenicity was evaluated in 3 studies in rats, and one study in rabbits, after oral administration.

In a study in which pregnant rats were dosed with 0, 13.8, 43.1 or 138 mg/kg bw/day orally, from day 6 to day 15 of pregnancy, and sacrificed on day 21 of pregnancy, no evidence of maternotoxicity and no embryotoxic, foetotoxic or teratogenic effects were found. A NOEL of 138 mg/kg bw/day was established.

In a second study, pregnant rats were dosed with 0, 13.8, 43.1 or 138 mg/kg bw/day orally from day 15 of pregnancy to day 21 post partum. The only adverse effect that could be found was a statistically significant decrease in litter weight and mean pup weight at day 21 post partum in the 138 mg/kg bw/day group. The NOEL was 43.1 mg/kg bw/day.

In a third study, groups of pregnant rats were dosed with 0 or 138 mg/kg bw/day orally. One group was treated from day 15 of pregnancy to day 10 post partum, the second group was treated from day 11 to day 20 post partum and the third group from day 15 of pregnancy to day 20 post partum. Body weights were monitored up to day 66 post partum. A statistically significant decrease in litter weight and mean pup weight at day 21 post partum in the long-term treatment group was found. After end of the lactation period the growth of the pups were essentially similar and the decreased pup weight was believed to be due to a decrease in milk production. An overall NOEL of 43.1 mg/kg bw/day was retained for the 3 studies.

In rabbits dosed orally with 0, 6.9, 27.6, 69.1 or 138 mg/kg bw/day from day 6 to day 18 of pregnancy, maternal toxicity was observed in all but not in the lowest dose group. The NOEL for maternotoxicity was 6.9 mg/kg bw/day. A dose related decrease in litter size and an increase in foetal loss was found at doses above 6.9 mg/kg bw/day. Some abnormalities and skeletal variants were observed in the 2 highest dose groups, which were considered to be secondary to the maternal toxicity. However, the frequencies of overall abnormalities in the pups were not statistically significant different between the groups. Treatment was discontinued after 8 days in the highest dose group and therefore no conclusive evaluation of potential teratogenic effects in rabbits could be made.

10. The mutagenic potential of omeprazole was tested in an Ames *Salmonella* test, an *in vitro* mouse lymphoma assay, *in vitro* assays for chromosome aberrations and polyploidy in human lymphocyte cultures an *in vivo* assay for chromosomal aberrations in mouse bone marrow cells and an *in vivo* mouse micronucleus test. No indication of a mutagenic effect was found and no indication of bone marrow depression was found.

11. Carcinogenicity was very thoroughly studied.

In rats, three 2-year studies using oral doses of 0, 1.7, 3.4, 13.8, 14.1, 44.0 and 140.8 mg/kg bw/day investigated the clinical and pathological changes observed after treatment with omeprazole. A dose-related increase in stomach weight and mucosa thickness was observed, strictly related to the gastrin concentration, corresponding to the known trophic effect of gastrin on the stomach. A time- and dose-related increase in both the incidence and the degree of severity of the Entero-Chromatofin-Like (ECL) cell hyperplasia including ECL-micronodules was observed. Also dose-related carcinoids in the gastric fundus were found as a continuum of endocrine cell hyperplasia. No evidence of carcinoid metastasis beyond the stomach was found.

A linear correlation between carcinoid incidence and the doses from 1.7 to 140 mg/kg bw/day was demonstrated and no long-term toxicological NOEL in rats could be established from these studies. The histidine-decarboxylase-(HDC)-activity and the plasma gastrin levels showed good correlation at all sampling times, and a dose-dependent increase in the mucosal histamine concentration was observed (in the rat the ECL-cell contains HDC and produces and stores histamine). At cessation of high-dose treatment at 55 weeks, the plasma gastrin levels, HDC activity, histamine content of the mucosa and the ECL-cell hyperplasia completely normalised to control levels. In antrectomised rats where the major site for gastrin production is removed, a direct correlation was seen between the plasma gastrin level and ECL-cell density as well as HDC- and histamine tissue levels. Exogenous gastrin showed the same dose-dependent changes in the stomach as seen with omeprazole and other acid-inhibitors.

Thus, the gastrin level was responsible for the changes in ECL-cell density, while omeprazole treatment as such was not likely to affect proliferation of ECL-cells. Female control rats were shown to have significantly lower plasma gastrin levels than males. Although similar high plasma gastrin levels were obtained after omeprazole treatment in males and females, the increase was greater in the females. It was concluded from the carcinogenicity studies in rats that hypergastrinemia secondary to acid inhibition by omeprazole results in a dose-dependent increase in ECL-cell hyperplasia, and micronodule formation, which may lead to dose-dependent formation of end-life ECL-cell carcinoids.

In dogs, a 1-year study and a 7-year study employed daily oral doses of 0.7, 5.5 or 28 mg/kg bw/day and 0.17 mg/kg bw/day, respectively. The only pathological changes occurred in the acid-secreting areas of the gastric mucosa. The changes consisted of a reversible atrophy of the chief cells in the dogs receiving 28 mg/kg bw/day and a rugal hypertrophy at doses above 5.5 mg/kg bw/day. Both findings are believed to be linked to the acid inhibitory effect of omeprazole. No changes were found in the lowest dose group. The NOEL was 0.7 mg/kg bw/day.

12. No specific studies on immunotoxicity were provided and there were no indications of immunotoxic potential in the toxicity studies.

Pharmacological studies in healthy human volunteers using doses up to 80 mg/person/day for 5 to 7 days were conducted and no significant adverse effects on the immune system were reported.

13. Based on the long-term toxicological NOEL of 0.7 mg/kg bw/day observed in the 1 year carcinogenicity study in dogs and applying a safety factor of 100, a toxicological ADI of 0.007 mg/kg bw, i.e. to 0.420 mg/per person, is established.
14. No data on the potential effects on human gut flora were provided. However, due to the nature of the substance, such data were not considered necessary.
15. There were no data on the potential effects on industrial food processing. Such data were not considered necessary for this type of substance.
16. The substance has been widely used in humans for 15 years, with a recommended dosage for adults of 20 mg per day for the treatment of gastric ulcers and 10 mg per day for the prevention of relapse. A number of study reports in healthy humans have been made available from the development of the product for human use. A study in healthy humans showed a low and non-statistically significant decrease in production of gastric acid at a dose of 10 mg per person per day. Eight healthy male subjects were given omeprazole for 5 days in daily doses of placebo, 5, 10, 20 and 40 mg. Four subjects were subsequently treated with 80 mg. Treatment periods were separated by at least 1 week. Gastric acid secretion and fasting plasma gastrin concentration were measured 6 hours and 24 hours after the final, fifth dose of omeprazole. Fasting gastrin concentrations were determined immediately before and after the fifth dose, 6 and 24 hours post-dose. Plasma gastrin concentration measured in the 5 mg per day dosage group was no different than placebo during both basal and peak acid output measurements, whereas a clear increase was observed after the 20 mg per day dosage regimen.

The NOEL was 5 mg/person/day, and applying a safety factor of 10 a pharmacological ADI of 0.0833 mg/kg bw, i.e. 5 mg/person/day is established.

17. A summary of reported adverse events has been forwarded together with expert reports covering post marketing safety studies in a large number of patients and epidemiological studies relating to the use in pregnant women. There was no evidence of an increased risk to patients and no specific pattern in the reported adverse events could be found. In pregnant women, three epidemiological studies compared women taking omeprazole or two other acid-inhibitors, during the first trimester, to groups of non-exposed women. There was no evidence of a higher incidence of malformations, miscarriage, fetal death or adverse effect on growth.
18. A toxicological ADI of 0.007 mg/kg bw, i.e. 0.420 mg/person was established based on the NOEL of 0.7 mg/kg bw/day observed in the 1-year carcinogenicity study in dogs and applying a safety factor of 100. This ADI is lower than the pharmacological ADI of 0.0833 mg/kg bw i.e. 0.5 mg/person day established on the basis of the NOEL of 5 mg/person day in humans applying a safety factor of 10. Therefore the toxicological ADI was considered the relevant ADI for assessing the risk for the consumers.
19. A residue depletion study in horses was performed using radiolabelled omeprazole formulated in a sodium carbonate/sodium bicarbonate buffer. An oral dose of 1 mg omeprazole/kg bw/day was administered for 7 days. Groups of 4 horses were slaughtered at 1, 24, 72 and 168 hours after the last dose and tissue samples were taken for residues analysis. The maximum concentrations of total radioactivity, 24 hours after administration, were: fat: not detectable; muscle: 23 µg equivalents/kg; liver: 420 µg equivalents/kg; kidney: 84 µg equivalents/kg. The highest concentrations of radioactivity were found at 1 hour after treatment in kidneys and liver; this is consistent with the routes of elimination for omeprazole.

The percentage of radioactivity extracted was 90 to 98% of total radioactivity with 43 to 61% found in urine and the remainder in faeces and cagewash. Low levels (less than 1%) of radioactivity were still detected in urine from 2 animals and in faeces of all animals at 168 hours after the last treatment.

After repeated daily oral administration for 7 days, no evidence of accumulation of radioactivity based on C_{max} values was found.

The maximum plasma concentrations (C_{max}) and the areas under the plasma concentration time curve were similar following one and seven daily doses. No significant difference ($p < 0.05$) in absorption and elimination following intravenous or orally administered omeprazole were seen between the first and seventh administration.

Conclusions and recommendation

Having considered that:

- an ADI of 0.007 mg/kg bw, i.e. 0.42 mg/person has been established,
- omeprazole is used in a small number of animals for infrequent or non-regular treatments,
- omeprazole is poorly absorbed after oral ingestion in humans,
- no accumulation in tissues is observed after prolonged administration;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish MRLs for omeprazole 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
Omeprazole	<i>Equidae</i>	For oral use only