



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CHLORPROMAZINE

SUMMARY REPORT

1. Chlorpromazine belongs to the phenothiazine group of compounds, which exert a sedative action by depression of the brainstem and connections to the cerebral cortex. Chlorpromazine is marketed as an injectable solution for intramuscular, intravenous and subcutaneous use in cattle, horse, sheep, goat, swine and domestic animals, generally in order to immobilise aggressive animals. All food producing species belong to the target species of this application. Chlorpromazine hydrochloride is used in human medicine as a tranquilliser.
2. A safety file was not provided. However, Joint FAO/WHO Expert Committee on Food Additives (JECFA), evaluated chlorpromazine in 1991. Data from this evaluation are summarized in paragraphs 3 to 13.
3. Chlorpromazine is a lipophilic compound with high intestinal absorption and wide distribution in the body. It is metabolised during passage through the intestinal wall and (mainly) in the liver. Major metabolic pathways are hydroxylation, oxidation, demethylation and glucuronidation. In man, 10-12 metabolites occur. N-oxide metabolites are reduced back to the parent compound in a number of species, including man. A sulfoxide is formed which possesses about one-eighth of the sedative action of the parent drug in dogs. The half-life in dogs was 6 hours. In the goat the concentration in milk was higher than in plasma. After intravenous and oral administration in the horse it was detectable in urine for up to 96 hours, with urinary recoveries of 10 and 27 %.
4. Oral LD₅₀ values in mice and rats were 135 and 210 mg/kg bw. Intravenous LD₅₀ values in mice, rats, rabbits and dogs were 20, 23-49, 16 and 30 mg/kg bw. Intraperitoneal LD₅₀ values were 115-136 mg/kg bw in mice and 71 mg/kg bw in rats.
5. Guinea pigs injected intraperitoneally with 30 mg/kg bw/day for 7 consecutive days showed local fibrous adhesions on peritoneum and intestinal surface, haemorrhagic areas on the peritoneal surface of the caecum and submucosal oedema, inflammatory changes and haemorrhages of the caecum. No other short-term or long-term repeated dose toxicity studies were available.
6. No single- or multi-generation reproduction toxicity studies were available. However, there were a number of other reproduction toxicity studies. Oral application of 16 mg/kg bw/day throughout pregnancy in mice resulted in a decreased number of pregnancies, increased number of days between mating and birth, reduced weight gain throughout pregnancy and effects on birth weight and several biochemical and organ weight parameters. In a second study in mice, oral application of 4 or 16 mg/kg bw/day throughout pregnancy resulted in several foetotoxic and materno-toxic effects in the highest dose group. The significance of a possible decrease of mean litter weight in the low dose group is not clear from the JECFA report. A single postnatal subcutaneous injection of 20 mg/kg bw up to the 10th post-natal day accelerated sexual maturation of male mice. Intramuscular administration of 5 mg/kg bw/day for 7 or 15 consecutive days in male rats caused alterations in reproductive organs and several biochemical changes. Single intraperitoneal administration of 2.5 mg/kg in 150 day old male rats affected copulation behaviour adversely. Intramuscular administration of 20 mg/kg bw on the 4th day of pregnancy in rats disturbed the late stage of pregnancy.
7. In an oral rat teratogenicity study with a dose of 0.585 mg/kg bw given on day 13, 14 or 15 of gestation, foetotoxicity and external foetal malformations were found. In an oral rat

teratogenicity study with doses of 5, 25 and 35 mg/kg bw/day during days 6 to 15 of gestation, foetotoxicity was found in the two high dose groups and malformations were found in one low dose pup. In a similar rat study with doses of 1, 3 and 9 mg/kg bw, no teratogenic or other dose related physical effects were found. However, at the two highest dose levels a non dose-related decrease of pup bodyweight was found and effects in an open field activity test. Oral administration of 20 mg/kg bw/day during days 6-20 of gestation in rats caused no effects on physical parameters, but several significant effects in developmental behavioural tests. In an intraperitoneal teratogenicity study in mice both tested doses of 1.8 and 9.2 mg/kg/day were teratogenic. In an intraperitoneal teratogenicity study in rats single treatment on day 14 of pregnancy with 100 mg/kg bw caused delayed ossification of several bones. In a subcutaneous teratogenicity study in rats, daily doses of 6 mg/kg bw/day on days 4-7 of gestation caused an increased number of deaths and behavioural changes in offspring.

8. In a chromosomal aberration assay in human lymphocytes, a SRCE test in human lymphocytes, an Ames test in *S. typhimurium* and a fluctuation test in *E. coli*, chlorpromazine caused positive mutagenic effects. In addition, JECFA stated that certain reactive metabolic intermediates are capable of binding to macromolecules, including DNA.
9. No carcinogenicity data were available.
10. Preimmunised and nonimmunised rats received 25 mg chlorpromazine/kg bw/day in the diet. No significant gross pathology was observed. Some animals fed a chlorpromazine diet showed signs of hepatotoxicity.
11. In man, therapeutic doses of chlorpromazine may cause side effects such as orthostatic hypotension, incidental cases of obstructive type of jaundice, leukocytosis and leukopenia, and more frequently, dermatological reactions. Large doses may interfere with human female pituitary-gonadal function.
12. JECFA concluded that, in view of the lack of relevant toxicological data, the long-term persistence of chlorpromazine in humans, the spectrum of additional effects of the drug, and the probability that even small doses can cause behavioural change, no ADI could be established. Furthermore, JECFA suggested that chlorpromazine should not be used in food producing animals.
13. Taking into consideration the conclusions and recommendations of JECFA and the fact that the CVMP received no relevant toxicological data, it was concluded that an ADI could not be established.
14. No residue data were provided to JECFA.
15. A pharmacokinetic experiment in pigs was provided to the CVMP. After single intramuscular administration of 1 mg/kg bw chlorpromazine in pigs the concentrations of the parent compound were measured in plasma, urine, kidney, liver, muscle and fat. C_{max} in plasma was 0.010-0.015 mg/l (at 0.25-1 hour post injection), C_{max} in urine was 0.107-1.316 mg/l (at 0.25-1 hour), C_{max} in liver was 0.0054 mg/kg (at 6 hours), C_{max} in kidney was 0.0129 mg/kg (at 1 hour), C_{max} in muscle was 0.0128 mg/kg (at 4 hours) and C_{max} in fat was 0.0279 mg/kg (at 1 hour). The tissue residue data were incompletely reported and could therefore not be assessed.
16. No other pharmacokinetic or residue data were provided.
17. For monitoring pig tissues an HPLC method with electrochemical detection was proposed. No adequate validation data were provided. The method was not described in accordance with an internationally recognised format (e.g. ISO 78/2). No analytical methods were provided for any of the other target species.

Conclusions and recommendation

Having considered that :

- no relevant toxicological data have been provided that and an ADI could not be established,
- insufficient residue data are available,
- JECFA recommended that chlorpromazine should not be used in food producing animals,

the Committee considered that residues of chlorpromazine are a potential risk to the health of the consumer and recommends its inclusion in Annex IV of Council Regulation (EEC) No 2377/90.