The European Agency for the Evaluation of Medicinal Products

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CHLORPHENAMINE

SUMMARY REPORT

1. Chlorphenamine (synonyms: chlorpheniramine, chlorprophenpyridamine, CAS No 113-92-8) is a racemic substance classified as an antihistaminic of the alkylamine group. Chlorphenamine is used in cattle, sheep, goats, pigs and horses at doses of 0.4 to 0.5 mg/kg bw/day for 3 to 5 days, intramuscularly in combination with antibiotics and occasionally with corticosteroids for treatment of respiratory diseases.

   Chlorphenamine is also used in humans at oral doses of 2 mg to 24 mg/person/day and intramuscularly, subcutaneously or intravenously up to 40 mg/person/day.

2. Chlorphenamine maleate is described as a histamine H_1-receptor antagonist. This drug also possesses, in different degrees, a variety of other actions, particularly within the central nervous system (transient hypotension or stimulation) like other substances of the pharmacodynamic group. The two isomers of chlorphenamine differ in antihistaminic potency: the *dextro*-form is 100 times more active than the *levo*-isomer and 2.5 times more than the racemic form. From the *in vivo* data provided, it was shown that a single oral administration of 0.128 mg/kg bw of chlorphenamine protected 50% of the guinea pigs in a test for antihistaminic activity. No pharmacological NOEL could be derived from this study. In another test for anaphylatic shock protection in guinea pigs a single oral dose of 0.51 mg/kg protected 38% of the animals and 0.11 mg/kg could be retained as a LOEL for this study.

3. Chlorphenamine maleate is rapidly absorbed in dogs after oral administration with a C_{max} between 92 and 279 µg/kg and a t_{max} of 30 to 45 minutes (dose of 100 mg/animal). The plasma half-life is 1.4 to 3.1 hours. Oral bioavailability is dose dependent from 9.4% (50 mg/animal) to 39.4% (200 mg/animal). N-Dealkylation is a major metabolic pathway and didesmethylchlorphenamine the major metabolite in urine of dog and rats. Fifty-four percent of the drug is recovered in urine. In rats, the highest tissue concentrations were observed in lungs, kidney and liver, and significant levels were also detected in brain and muscle.

   Two pharmacokinetic studies in cattle (12 animals, 6 per sex) have been conducted at a dose rate equivalent to 0.5 mg/kg bw. Following intravenous administration, the concentrations of chlorphenamine maleate in plasma declined from 365 µg/kg to the limit of quantification (1 µg/kg) 24 hours after the administration. The elimination half-life is 2.11 hours and the mean residence time (MRT) 2.35 hours. Body clearance is 1.315 l·kg/hours and the volume of distribution slightly above 3 l/kg. Via the intramuscular route, a mean C_{max} of 142 µg/kg is observed with a t_{max} of 28 minutes. Then, the concentrations declined to reach 60 and 12 µg/kg at 2 and 8 hours post injection, respectively, and the levels were below the limit of quantification (1 µg/kg) 24 hours after intramuscular injection. The mean residence time is 3.58 hours and the intramuscular bioavailability 100%.

   These data indicate excellent absorption and distribution, as well as a rapid elimination of chlorphenamine; the elimination half-life is short and the compound widely distributed.

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4. Oral LD_{50} values for the chlorphenamine maleate ranged from 118 to 264 mg/kg bw in rats, mice and guinea pigs. After intraperitoneal administrations, the LD_{50} were in the magnitude of 110 mg/kg bw in mice and rats.

   No information on the toxicity of the individual isomers was provided, but dexchlorphenamine (the dextrorotatory isomer of the racemate) has approximately twice the activity.

5. Although repeated dose toxicity tests were performed in rats (3-generation study), dogs (6-month toxicity study) and monkeys (7-week study), it was not possible establish NOELs due to the poor quality of the documentation provided.

6. A 13-week study was conducted in rats treated 5 days per week with chorphenamine doses of 0, 3.75, 7.5, 15, 30 and 60 mg/kg bw/day. All rats survived to the end of the study. Lower final bodyweights were observed in the male rat 15 mg/kg bw group. A NOEL of 7.5 mg/kg bw/day was established based on the decreased bodyweight in males.

7. In a reproduction study CD rats received by gavage 0, 5, 10 and 20 mg/kg bw chlorphenamine maleate. Males were dosed daily for 63 weeks, plus a 3-week mating period. Females were treated 21 days before mating, until sacrifice at either 14 days of gestation or 21 days after parturition. A NOEL of 5 mg/kg bw of chlorphenamine maleate (3.5 mg/kg bw of chlorphenamine) was established based on post natal survival of the pups.

8. Chlorphenamine gave negative results in a battery of 2 *in vitro* tests (*Salmonella*-microsomal assay and mouse lymphoma test). A further *in vitro Salmonella* microssomal assay with nitrosation of chlorphenamine did also not produce mutagenic response. In Chinese hamster ovary cells an increase in chromosomal aberrations was only observed at high concentrations (500 µg /ml). Overall, it can be concluded that chlorphenamine does not present a mutagenic potential.

9. In two 2-year mice carcinogenicity studies in F344/N rat and B6C3F1, no evidence of carcinogenicity was seen in either sex when the compound was administered 5 days a week in water at dosages of 0, 15 and 30 mg/kg bw(male rats), 0, 30 and 60 mg/kg bw(female rats), 0, 25 and 50 mg/kg bw (male mice) and 0, 100 and 200 mg/kg bw (female mice).

10. Bioavailiblity of chlorphenamine in humans is reported to be 25 to 50%.

    Some adverse effects like irritation after injection, hypotension, stimulation of central nervous system, blood dyscrasias (agranulocytosis, thrombocytopenia, pancytopenia) have been reported in humans. Extrapyramidal effects were also reported after oral administration in man. Adverse side effects such somnolence, dizziness, tachycardia and gastro intestinal disorders were reported. More than half of these effects is qualified as general disorders with a great majority simply being an insufficient response to treatment.

11. Applying a safety factor of 100 to the LOEL of 0.11 mg/kg bw retained from the test for anaphylatic shock protectiom in guinea pigs, a pharmacological ADI of 0.0011 mg/kg (i.e. 0.066 mg/person) was established. The safety factor of 100 is justified due to the sensitivity of the test. This ADI is 30 times lower than the lowest human therapeutic dose of 2 mg/person.

12. Based on the toxicological NOEL of 3.5 chlorphenamine mg/kg bw (5 mg chlorphenamine maleate/kg bw) retained from a 2-generation study in rats, a toxicological ADI of 0.035 mg/kg bw (i.e 2.1 mg/person) was established applying a safety factor of 100.

13. In a study carried out in order to follow the decrease of residues at the injection site, 8 animals received 2 intramuscular administrations of 0.5 mg chlorphenamine/kg bw 24 hours apart at 2 different sites. Twenty four hours after administration all the concentrations were below 25 µg/kg except for one animal (175 µg/kg). At 48 hours chlorphenamine could be measured in one animal (89 µg/kg) and at 72 hours all the concentrations were below the limit of quantification (25 µg/kg).

No information was available for other edible tissues. However, considering that chlorphenamine is rapidly eliminated this information was not considered necessary. Furthermore, as chlorphenamine is only used in combination with antibiotics or corticosteroids the small amount of residues which might be found in food products of animal origin will not present any potential risk for the consumer due to the withdrawal period to be established for the other active substances in the medicinal product.

14. A validated analytical method to determine chlorphenamine residues in muscle is available.

Conclusions and recommendation

Having considered that:

- an pharmacological ADI of 0.0011 mg/kg bw (i.e. 0.066 mg/person) was established,
- treated animals are unlikely to be sent for slaughter immediately after treatment,
- chlorphenamine is rapidly eliminated and residues at the injection site only occasionally were detected at the injection site 24 hours after treatment, which in a worst case scenario would still remain below the ADI;

the Committee for Veterinary Medicinal Products concluded that there is no need to establish an MRL for chlorphenamine and recommends its inclusion in Annex of II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Chlorphenamine	All mammalian food producing species	