



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

POLICRESULEN (METACRESOL SULPHONIC ACID-FORMALDEHYDE)

SUMMARY REPORT

1. Policresulen, the dihydroxy - dimethyl - diphenylmethane disulfonic acid polymer $(C_8H_9O_4S)(C_8H_8O_4S)_n(C_7H_7O_4S)$, which is more known as metacresol sulphonic acid-formaldehyde, results from the poly-condensation of metacresol sulphonic acid with formaldehyde.

Policresulen is authorised for veterinary medicine in cattle, sheep, horses, pigs, dogs and cats.

2. Policresulen is a local haemostatic and antiseptic substance which can be applied without being diluted (2 % gel) onto the skin or diluted (solutions containing 0.36 % to 7.20 % of active substance) for the cleanings of infected or inflamed wounds especially in the urogenital area. Policresulen has a strong bactericidal effect on pathogenic micro-organisms (gram-negative, gram-positive and yeasts).
3. Due to complex nature of the polycondensation product, pharmacokinetic studies were carried out with ^{14}C -Dicresulen in different animals (rats, dogs and rabbits). In all species studied, the systemic absorption after oral administration of 5 to 30 mg/kg b.w. was less than 10%.

In rats, after an IV administration of 5 mg/kg b.w. of ^{14}C -Dicresulen, 86.7% of radioactivity were recovered in urine and faeces within 72 hours after administration. After oral administration of 5 or 30 mg/kg b.w, these percentages were 104% and 98.6 % respectively.

In dogs, 90% of the dose were recovered within 72 hours following a single intravenous administration : 56% in the urine, 34% in the faeces. After oral administration of 5 mg/kg ^{14}C -Dicresulen, only 5% of the dosage were recovered in the urine and 85% in the faeces. This confirms the low systemic resorption after oral administration.

4. The oral LD50 values were close to 2500 mg/kg b.w (mice) and to 3500 mg/kg b.w (rats). The intravenous LD50 values ranged from 340 to 380 mg/kg b.w for mice and from 390 to 420 mg/kg b.w. for rats. There was no difference in lethality between males and females.
5. Two three-month oral toxicity studies were carried out, the first one, in rats (150, 450, 1350 mg/kg b.w) and the second one, in dogs (100, 300 and 900 mg/kg b.w). In rats, the highest dose involved motility reduction, chromodacryorrhea, reduced the body weight and increased the salivation. A reduction of the thymus weight and a decrease in the weight of the prostate and of the seminal vesicles were also observed. (NOEL: 150 mg/kg b.w).

In dogs, 2/9 animals died from the group with the highest dosage. Few cases of hypersalivation 2 hours after administration were reported in the 300 and 900 mg/kg b.w. group. Gastrointestinal disorders with vomiting and/or diarrhoea after administration and dose dependent were observed (NOEL: 100 mg/kg b.w).

6. After intra-uterine infusion with a solution at 36% of Policresulen (at different dilutions: 2%, 4% and 8%) to cows, no systemic disorders was reported after the clinical examinations.

The examination of the skin compatibility in mice using 3 preparations of a solution at 36% of Policresulen (at different dilutions: 4%, 12% or 36%) showed no undesired or adverse effects, each preparation being applied on shaved skin daily for 15 days.

7. Two oral teratogenic studies were performed in rats (100, 300, 900 mg/kg b.w) and in rabbits (100, 300 mg/kg b.w). In the rat study, the weight gain of the dams and the average weight of the living foetuses were reduced in the highest dose group (900 mg/kg b.w). The fertility was not inhibited by the treatment. Policresulen was non-teratogenic. The NOEL was 300 mg/kg b.w. based on the absence maternal and foeto-toxicity.

In the rabbit study, the mean body weight of foetuses slightly decreased in the 300 mg/kg group, 100 mg/kg b.w being the NOEL.

8. Policresulen was not mutagenic in Ames test.
9. Policresulen is used for the treatment of gynaecological and proctological disorders in humans since 1938. No adverse effects have been published up to now in the literature.
10. A NOEL of 100 mg/kg b.w could be retained from the three month oral toxicity study performed in dogs. With a safety factor of 100, the following acceptable daily intake of 1 mg/kg/day i.e 60 mg/person could be established.
11. No information after dermal application was provided for the target species. However, the injection of 7.2 mg ¹⁴C-Policresulen in the horn of 8 rabbit's uterus showed that the drug was rapidly absorbed via the uterine mucosa. In tissues, the levels of radioactivity were close to the limit of sensitivity of the method at 72 hours after the administration.

CONCLUSION AND RECOMMENDATION

Having considered that :

- Σ the toxicity of Policresulen is low,
- Σ the absorption of the drug after topic administration is very low,
- Σ this drug is rapidly excreted.

Having also considered the criteria laid down by the Committee for inclusion of substances into Annex II of the Council Regulation (EEC) N° 2377/90 and that:

- Σ Policresulen is used in a small number of individual animals and for infrequent and non-regular treatment,
- Σ Policresulen is intended for only local and short time period treatment,

The Committee for Veterinary Medicinal Products concluded that maximum residue limits for tissues are not necessary to ensure consumer safety and recommends the inclusion of Policresulen in Annex II of Council Regulation (EEC) No 2377/90 EEC as indicated in the following table:

Pharmacological active substance(s)	Animal species	Other provisions
Policresulen	All food producing species	For topic use only