



## COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

### ALLANTOIN

#### SUMMARY REPORT

1. Allantoin (5-ureidohydantoin [2,5-dioxo-4-imidazolidinyl]urea; CAS 97-59-6) is used topically to stimulate healing of wounds. It is administered cutaneously as a spray or a balm to cattle, sheep and horses. Preparations containing 1.4 to 2% allantoin are applied to the injured skin area two or three times per day.
2. There are no data which substantiate the pharmacodynamic properties of allantoin. Its mechanism of action is unknown.
3. Studies in cattle, sheep, horses and humans showed that allantoin is an endogenous substance. The endogenous plasma levels vary considerably with the conditions (e.g. diet, exercise) of the individual.
4. In cattle, sheep and horses, allantoin is the end product of purine metabolism. In contrast, the end product of purine metabolism in humans is uric acid. One of the suggested functions of uric acid in human body fluids is to act as an antioxidant. In humans, certain reactive oxygen species may oxidise uric acid to allantoin.
5. Pharmacokinetics is similar in cattle, sheep and horses. Allantoin is rapidly cleared from the plasma. Its half-life is in the range of 1 to 2.5 hours. Allantoin is not metabolised to a measurable extent. Urinary clearance is the major excretion route, accounting for about 70 to 80% of the total clearance in the target species. Minor excretion routes are the milk in cows and saliva in sheep (accounting for about 2 and 0.3%, respectively, of the total clearance).
6. Upon oral administration by stomach tube, the LD<sub>50</sub> in rats is more than or equal to 10 g/kg bw. Upon dermal application to the normal and abraded skin, the LD<sub>50</sub> in rats is more than or equal to 5 g/kg bw.
7. No studies on repeated dose toxicity and reproductive toxicity were submitted. Such studies are not needed in view of the endogenous nature of allantoin and the anticipated low exposure of consumers to allantoin residues in food products of animal origin.
8. Allantoin, either alone or after nitrosation, was not mutagenic in vitro to *Salmonella typhimurium* strains, with or without liver S9 activation. Further mutagenicity tests are not required in view of the endogenous nature of allantoin.
9. Feed containing 0.2% allantoin, with or without 0.2% sodium nitrite, was given to male and female F344 rats for 106 weeks. The tumor incidence in allantoin-treated animals did not differ significantly from that found in untreated or nitrite-treated controls. Further carcinogenicity tests are not required in view of the endogenous nature of allantoin and the lack of mutagenicity findings.
10. Allantoin shows no sensitising potential in guinea pigs. In rabbits, there are no signs of primary skin irritation (tested on normal and abraded skin) or eye irritation.

11. In healthy human volunteers, the mean plasma concentration of allantoin is about 2-3 mg/l. During exercise, the plasma allantoin concentration rapidly increases about 2-fold and remains elevated. In human muscle, urate is oxidised to allantoin during exercise. The concentration of allantoin in muscle increases from a resting value of about 5000 µg/kg to about 16000 µg/kg immediately after short-term exhaustive cycling exercise.
12. No information on residues of allantoin and their depletion following treatment of food producing animals was provided.

### Conclusions and recommendation

Having considered the criteria layed down by the Committee for Veterinary Medicinal Products for the inclusion of substances in Annex II of Council Regulation (EEC) No 2377/90 and in particular that:

- Allantoin is a normal component of the diet in humans,
- Allantoin is a substance of endogenous origin present in the body of both target animals and man,
- Allantoin is part of basic metabolic pathways; therefore, no accumulation is expected,
- Allantoin is generally recognised as safe for humans,
- Exogenously administered allantoin is rapidly excreted,
- Allantoin is intended for topical use only;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish a MRL for allantoin 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
Allantoin	All food producing species	For topical use only