COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

MELATONIN

SUMMARY REPORT

1. Melatonin is a natural indoleamine hormone produced (from serotonin) by the pineal gland of the brain of humans and other mammals. Chemically, it is not related to the steroid or peptide hormones. Its biosynthesis is inhibited by lighting and stimulated by darkness.

   Melatonin is used as a subcutaneous slow-release implant (behind the ear) of ewes, 30 - 40 days before early season mating, to improve reproductive performance. The implant should be administered to a tissue which would not reach the consumer.

   Seasonally-breeding animals, such as sheep, time their mating activity to occur one gestation-length before the season of optimal food supply. In anoestrus ewes, administration of melatonin induces the endocrine and behavioural changes normally associated with shortening day-length.

2. In laboratory animals, relatively high doses had to be administered in order to produce pharmacological effects such as sedation, analgaesia and anticonvulsant activity. In humans melatonin had short-acting mild sedative properties. It also had endocrine effects ; a NOEL of 0.04 mg/kg bw per day for these was established in a study in which adult males received repeated oral doses for up to 2 months.

   In sheep, melatonin was well absorbed after subcutaneous administration but was more slowly absorbed after oral administration . It was well distributed and around 60% of the melatonin in blood was loosly bound to albumin. In sheep, humans and rats, melatonin was metabolised chiefly to 6-hydroxymelatonin followed by conjugation with sulphate or glucuronide and excretion predominantly in the urine.

   No classical repeat-dose toxicity studies were carried out with melatonin. However, some information on the effects of repeated dosing was available from pharmacology and studies designed to investigate endocrinological end-points.

   Melatonin was well tolerated in the target species, sheep.

   Melatonin crosses the placenta in sheep. Residues of melatonin have been found in the chord blood of humans. In a published study, melatonin was not teratogenic in the mouse. Information on the use of melatonin in sheep during pregnancy indicated that it was not teratogenic in this species. Melatonin did not affect the oestrus/menstrual cycle in rats/marmosets.

   Melatonin was not mutagenic in a non-replicated *in vitro* mutation assay for gene mutation in bacteria. No other mutagenicity studies were carried out and there were no carcinogenicity bioassays. A review of the literature indicated that melatonin had a possible cancerostatic effect.

3. Melatonin was employed in several human volunteer studies and clinical trials. These included studies designed to examine its possible value in the treatment of jet lag, psychiatric disorders, cancer and Parkinsonism.

4. An ADI of 0 - 0.004 mg/kg bw per day for melatonin may be calculated by applying a safety factor of 10 (to account for variation within the human population) to the no-observed-hormonal-effect level of 0.04 mg/kg bw per day which was established in a repeated oral dosing study in humans.

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5. The use of the drug in sheep increased the residues of melatonin in most tissues, over the endogenous melatonin concentrations. However in many cases, the residues found were of a similar order of magnitude to the endogenous concentrations arising during the peak production time, during the night.

6. Because it was not possible to distinguish residues of endogenous melatonin from the residues arising from the use of the product, it was agreed that it would be inappropriate to elaborate MRLs for melatonin. It was noted that there was a large safey margin between the ADI and the likely intake of residues from food commodities of animal origin.

   Melatonin should therefore be included in Annex II of Council Regulation (EEC) N° 2377/90.

7. Analytical methods based on RIA were available to measure the residues of melatonin in tissues. Methods based on GC-MS, capable of monitoring residues of the metabolite 6-hydroxymelatonin in plasma and urine, had also been published. The analytical methods were not fully validated.