The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ETIPROSTON TROMETHAMINE

SUMMARY REPORT

Etiproston tromethamine is a synthetic analogue of prostaglandin PGF 2 alpha. It is a luteolytic agent indicated for parenteral use in the sow and the cow.

PHARMACOLOGY

Absorption

Is rapid in the species examined.

In rats it is rapid following intravenous, intramuscular or subcutaneous administration with an equally rapid decline in plasma levels over 24 hours.

In cattle following intramuscular administration, peak levels were achieved in 30 minutes to 2 hours following injection, the magnitude of the peak varied from 1.85 to 7.88 ng/ml in plasma.

In pigs using the intramuscular route the time to peak levels varied between individuals from 10 minutes to 3 hours. Peak levels varied from 3.5 to 13.2 ng/ml in plasma.

As absorption from the gastro-intestinal tract is limited and pharmacological activity following oral administration is negligible absorption by this route was not studied. Results of the 4-week and 13-week toxicological studies tend to confirm this observation. Signs of toxicity were seen only in the 13-week study in the dog, these were isolated incidences of vomiting and diarrhoea which were considered to be attributable to the local effect of etiproston. There were no adverse clinical signs observed in rats. In reproductive toxicity studies (using the intramuscular route) and in tests for embryotoxicity and teratogenicity no treatment-related effects were noted.

Distribution

Following administration of radio-labelled etiproston to the rat, liver and kidney show the highest levels while lung levels were low but consistent throughout a 24-hour period. Less than 1% of total radioactivity was recorded in all tissues by 4 hours. In the sow and cow liver and kidney were the main target organs.

Metabolism

Is both rapid and extensive in cattle and pigs. Less than 20% of the administered dose remains unchanged.

The degree to which etiproston is metabolised in cattle and pigs is both rapid and extensive. Less than 20% of the administered dose remains unchanged. Metabolism is by β-oxidation, the major metabolite is the tetranor derivative in cattle and the dinor derivative in the sow.

Elimination

Is mainly in the urine in the rat, cow and pig. In the cow first traces in urine were found at 1 hour after administration. By 7 hours first traces were found in faeces. Levels in milk were low or below the detection limits at all sampling times. In the pig 46% of the dose was found in the urine 4 hours after administration by the intramuscular route. Elimination in faeces was low.

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TOXICOLOGY

Acute toxicology of etiproston is low .

Subacute studies in rats at 100, 300, and 1000 µg/kg/day revealed no clinical findings related to treatment. Post-mortem showed a slight increase in weight of liver, heart and spleen but no histopathological changes were noted. A NOEL of 300 µg/kg/day is proposed from this study.

In dogs subacute studies using dosage rates of 0.1, 0.3 and 1.0 mg/kg/day produced clinical signs including passing of abnormal faeces and isolated incidence of vomiting, these effects are attributed to the local action of etiproston. There was no significant increase in organ weights. No histopathological changes were noted. A NOEL of 0.3 mg/kg/day is proposed.

Tests for embryotoxicity and teratogenicity in the rat and rabbit revealed no findings of significance beyond the inherent luteal and uterine effects of this class of compounds.

A series of mutagenicity studies including Ames test, HPRT Locus Mutation assay, Mouse Micronucleus tests and a Chromosome Aberration test were conducted. With the exception of the Chromosome Aberration test where positives were found at the highest doses with activation all tests were negative at all dosage rates.

There were no carcinogenicity studies presented. These were considered unnecessary as the substance has no structural relationship to known carcinogens and is considered to be nonmutagenic.

RESIDUES

In cattle, a study using the recommended dosage rate showed liver, kidney and muscle (except injection site) below the limit of detection at 36 hours. Injection site studies showed 1 of 4 samples positive (1.16 ng/g tissue) at this time. For milk 2 samples exceeded the detection limit (0.84 ng/ml) at the first milking, thereafter all samples were negative.

In the pig following administration at the recommended dosage rate levels in organs and tissues were just over the detection limit by 24 and 48 hours. Concentration at injection site was slightly higher but variable. At 6 hours 1 animal had detectable levels of 79.3 ng/g of total radio-activity. By 72 hours 1 injection site sample showed a level of 12.1 ng/g. Apart from the injection site the decline in etiproston levels in other tissues was rapid.

Due to the low toxicity, rapid metabolism and depletion of etiproston from the animal body an MRL is not deemed necessary. The compound is proposed for inclusion in Annex II.