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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DINOPROST TROMETHAMINE

SUMMARY REPORT

1. Dinoprost tromethamine is a synthetic analogue of prostaglandin. F2α is an autocrine hormone present in many mammalian tissues.

2. It is used to cause luteolysis in the cow, sow and mare. It is given as a single injection by im or sc routes, the recommended dosage rate is 25 mg cow; 10 mg sow and 5 mg mare. It is rapidly absorbed from the injection site.

3. It has an extremely short half life of only a few minutes, it is almost completely cleared following one or two passages through the liver and/or lungs.

4. No accumulation of dinoprost or residues have been detected in blood following repeated daily injection to cattle.

5. It is of low acute oral and parenteral toxicity

   Oral LD_{50} mice 1,300 mg/kg male, 1,550 mg/kg female
   rats 1,170 mg/kg male, 1,210 mg/kg female

   iv administration of 402 mg/kg dinoprost tromethamine did not produce lethal effects in mice.

6. In repeat dose studies in rats - doses of 3.2 mg/kg/day by the iv route for 28 days produced no evidence of toxicity; by the sc route, first signs of intolerance in a 6 day study were observed at 32 mg/kg, these were diarrhoea and depression. Dermal application over 37 days produced no observable toxic effects.

   In the dog doses of 0.6 mg/kg/day for 30 days by the iv route produced no signs of toxicity; oral doses of up to 30 mg/kg/day for 5 days were judged non toxic.

   In the monkey at 15 mg/kg/day by continuous iv infusion for two weeks dinoprost was considered non toxic (there were slight, non significant changes in circulating lymphocytes, a slight increase in blood urea nitrogen, a slight lowering of blood cholesterol and an increase in blood fibrinogen levels).

7. From a 90 day oral study in monkeys the toxicological NOEL was determined to be 8 mg/kg. The NOEL for significant pharmacological effect was 1.25 mg/kg.

8. In normal men and normal non pregnant women oral doses of up to 30 mg did not produce any obvious effect on the gastrointestinal tract, on pulse rate or on blood pressure.

   Oral doses of 25 mg caused uterine contractions in early pregnancy.

   An oral dose of 5 mg given, in late pregnancy (weeks 38-40) failed to induce parturition, but increase amplitude and frequency of uterine contractions.

   In a study using various repeat doses the minimal cumulative dose to induce labour was 30 mg while the maximal oral dose was in excess of 115 mg dinoprost.

9. Dinoprost is a bronchoconstrictor in humans. However hundreds of patients have been infused with dinoprost to induce abortion or labour without bronchial complications.

   Patients given dinoprost orally in a number of studies were not observed to have any bronchial distress.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel: (+44-171) 418 84 00 Fax: (+44-171) 418 84 16

10. Some teratogenic changes were noted in rats and rabbits exposed to high doses of dinoprost tromethamine by the sc route (estimated to be 30 x recommended dosage rate) for 3 days. It is likely that those effects are produced by the physiological activity of dinoprost which results in foetal hypoxia.

11. The substance was non mutagenic, but only 2 test systems were used - Ames test and DNA Damage/Alkaline Elution in Chinese hamster lung fibroblast cells.

12. The most sensitive organ to oral administration would appear to be the uterus of the near term pregnant woman, a dose of 5 mg produces a minimal response in this organ.

    Taking 10% of this dose and a safety factor of 10 an ADI for dinoprost tromethamine is 0.83 µg/kg bw (corresponding to 50 µg for a 60 kg person),

    Data on absorption, distribution, metabolism and excretion and residue data show that dinoprost is rapidly removed from the animal body.

    Given these facts it is concluded that an MRL is not required and dinoprost tromethamine is considered a suitable compound for inclusion in Annex II of Regulation 2377/90.