1. Tiaprost is a synthetic analogue of prostaglandin F2α from which it differs by modification of the lower β side chain. It’s formula is 15αβ-16-(3-thienyloxy)-(17-20) tetranor-PGF2α. It is presented as a tromethamine salt of the racemic form (15α/15β-epimers in the ratio 1:1). The α and β epimers differ by the position of the -OH group on position 15. It is used to treat suboestrus, chronic endometritis and to abort mummified foetuses and to induce parturition. In cattle, horses and pigs it is used as an oestrus-synchronising agent. A single intramuscular injection is indicated at the following dosages; cattle 750 µg (1.0 to 2.5 µg/kg bw), horses 450 µg (0.6 to 1.125 µg/kg bw), pigs 300 to 600 µg (2.0 to 3.0 µg/kg bw), sheep 150 to 225 µg (2.5 to 3.75 µg/kg).

2. The pharmacokinetics and metabolism of tiaprost was investigated in rats, mares, cows, and sows using 14C radiolabelled compound.

An intravenous dose of 100 µg/kg bw was administered to rats. Elimination of the compound took place in a three phasic process with estimated half lives of 0.09, 0.40 and 5.60 hours. Between 87.6% to 94.6% of the administered dose was excreted within 72 hours, the urinary route accounting for 67% of the administered dose. Concentrations of the compound were found in all organs examined 15 minutes post administration with highest levels found in liver and kidney. However, at two hours post administration, levels had fallen to between 4% to 12% of the previously measured levels. At 3 days post administration levels in all tissues, with the exception of the kidney, were at or below limit of detection (0.10 µg/kg).

Tiaprost was administered intramuscularly to two mares at a dose rate of 0.00075 mg/kg bw. Peak levels in blood and plasma were measured between 1 and 2 hours post administration. In one of the mares, a second peak in both blood and plasma was measured 2.5 hours post injection. Blood levels fell below the limit of detection (0.00016 µg/ml) 3.5 to 4 hours post injection whilst plasma levels fell below the detection limits (0.00007 µg/ml) after 7 hours with τ of 1.6 to 1.8 hours. Between 56.5% and 62.8% of the administered dose was excreted in the urine over the time period measured. 97 to 99% of this had left the body within 24 hours.

Following a single intramuscular administration of tiaprost at a dose rate of 0.002 mg/kg bw to a cow, highest blood and plasma levels were recorded 30 minutes post administration, with a second peak, half as high as the first, 90 minutes post administration. Levels fell below the limit of detection (0.0001 µg/ml) after 4 hours (blood) and 7 hours (plasma). A half-life from second peak to 4 hours post administration of 1.1 hours (blood) and 1.2 hours (plasma) was observed. Within the trial period (24 hours) 84% of the dose was excreted renally (86% of this amount within 4 hours of administration), 18% faecally, and 0.05% with the milk. Total recovery amounted to 102.2%. 

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In a further trial tiaprost was administered to two sows at a dose rate of 0.003 mg/kg bw intramuscularly. Maximum levels (close to 0.005 µg/ml) were detected in blood and plasma after 15 minutes. The plasma concentrations decreased with a terminal half life elimination time of 99 hours. Excretion was mainly renal with between 82.4% and 86.7% of the dose recovered in the urine, whilst 15% appeared in the faeces. Total recovery over 72 hours amounted to 101.4%.

3. Metabolism and biotransformation were studied in the rat and in the pig, the cow and the horse. Administration was intravenous in the rat and the investigation included urine, plasma and faeces whilst administration was intramuscular in the pig, cow and horse and urine was investigated. In addition to recovery of the parent compound, a tetranor compound of tiaprost was identified in all species studied which was the principal metabolite in plasma, urine and faeces of the rat, and in the urine of cattle and the pig. The 15-keto compound of tiaprost was found in rat urine in small amounts. In the horse, a sulphuric acid conjugate of the compound was identified as the main metabolite. This conjugate was not detected in the other species studied.

4. Acute toxicity studies were carried out in rats, mice and guinea pigs. In rats LD₅₀ values were 22.9 mg/kg bw after oral administration, and 2 mg/kg bw after intramuscular or intravenous administrations. Toxic symptoms which developed included decreased motility, tachypnoea and hyperpnoea occurring after 10 minutes and convulsions and death taking place between 15 and 90 minutes post administration.

In mice LD₅₀ values were 15.3 mg/kg bw after oral administration, 9.8 mg/kg bw after intramuscular administration and 1.60 mg/kg after intravenous administration. Toxic symptoms which developed included decreased motility for several days, tachypnoea and hyperpnoea, discoordination and death.

In the guinea pig doses of 0.1 mg/kg bw/day and 0.4 mg/kg bw/day subcutaneously produced drowsiness and inertia with one half of the animals in the high dose group being so affected (total number of animals in this trial not indicated).

5. In a tolerance study, cattle displayed no signs of intolerance after intramuscular administration of 40 mg/animal. This dosage level was considerably greater than the therapeutic dosage level.

6. A subacute toxicity study was performed in rats given tiaprost intravenously at dose levels of 0.004, 0.02 and 0.1 mg/kg bw/day for 30 days using 10 male and 10 female animals per dose group (one half the high dose group was given 0.5 mg/kg bw/day after 15 days of the trial). One rat in the 0.100 mg/kg bw/day group and 8 rats in the 0.5 mg/kg bw/day died. The cause of death could be ascertained neither macroscopically nor histologically. The only morphological effects noted were necroses of myocardial fibres in half of the rats receiving 0.5 mg/kg bw/day but this was not considered to be the cause of death. Isolated cases of enlargement of the renal pelvis in individual rats was thought to be caused genetically in the strain of rat used in the study. At the 0.5 mg/kg bw/day dose level, tachypnoea and decreased motility were noted after the daily injection. Male rats on the intermediate and high dose levels displayed decreased serum alkaline phosphatase levels. A NOEL of 0.02 mg/kg bw/day was retained.

7. Two 3-month repeated toxicity studies were carried out in rats and pigs.

Tiaprost was administered to rats orally (per gavage) at three levels: 0.02, 0.2 and 2 mg/kg bw/day for 90 days (15 male and 15 female per group and as controls). No haematological values measured were outside the range of deviation for the breed of rat used. Animals on the high dose level showed significantly higher weights (reversible) for heart, liver and ovaries. No morphological changes were noted on post mortem. A NOEL of 0.2 mg/kg bw/day was retained.
Pigs were given three levels of tiaprost orally (in the feed) 0.012, 0.060 and 0.3 mg/kg bw/day for 90 days (5 male and 5 female pigs per dose level and as controls). At the two highest dose levels weight increase, particularly in males, declined, and feed intake was reduced. Hindquarter weakness and increased incidence of diarrhoea was noted at the high dose level. Significant differences in clinical-chemical serum values between the high and control dose groups were noted: decreased inorganic phosphorus, bilirubin and serum glutamic-pyruvic transaminase (SGPT) and increased blood urea-nitrogen and uric acid indicative of a catabolic effect. Increased weight of several organs (adrenal gland, brain, pancreas, and thymus) was noted following dissection of animals on the high dose level. Other organs examined showed no changes in weight in comparison with the controls. The NOEL was 0.012 mg/kg bw/day.

8. Two mutagenicity studies were conducted. A Salmonella-microsomal assay was performed using 5 strains of Salmonella typhimurium auxothrophic for histidine (TA98, TA 100, TA 1535, TA 1537, TA 538) and one strain of Escherichia coli auxotrophic for tryptophane (WP2 uvrA) with levels of compound from 20 \( \mu \)g/ml up to 10 000 \( \mu \)g/ml. No point mutation inducing properties were noted. An in vivo micronucleus test in mice at levels 2.5, 25 and 250 \( \mu \)g/kg bw intravenously (5 male and 5 female animals per dose group and as controls) was negative. The are no structural alerts for this category of compound which would indicate mutagenic potential. It was concluded that tiaprost is unlikely to be a mutagenic compound.

9. No reproduction or teratogenicity studies were provided. However, tiaprost belongs to the group of prostaglandin substances, which have not shown any teratogenic effects either in laboratory species or in the target species.

10. No data regarding immunotoxicity was provided. Prostaglandins are not known to have immunotoxic properties.

11. No data has been provided regarding human use of tiaprost.

12. Using a NOEL of 0.012 mg/kg bw/day from the most sensitive toxicological study (90-day oral toxicity in pigs) and a safety factor of 100, a toxicological ADI of 0.0012 mg/kg bw (0.0072 mg/person) can be established. This safety factor was considered as sufficient due to the hypersensitivity of the species considered (16-fold more sensitive than rats).

13. Following a single intramuscular administration of radiolabelled tiaprost at a dose rate of 0.002 mg/kg bw to a cow a concentration of 0.08 \( \mu \)g equivalents tiaprost/kg was detected in the milk obtained between 4 to 19 hours post injection. Following slaughter 24 hours after commencement of the trial, examination of a wide spectrum of organs and tissues post mortem revealed that 0.49 \( \mu \)g equivalents tiaprost/kg levels could only be found in the kidney. In all other tissues the concentrations were lower than 0.10 \( \mu \)g equivalents tiaprost/kg. The injection site was not included in this examination.

14. In a further trial radiolabelled tiaprost was administered intramuscularly to two sows at a single dose rate of 0.003 mg/kg bw. One day after administration detectable concentrations were found in kidney (1.44 \( \mu \)g equivalents tiaprost/kg) and liver (0.26 \( \mu \)g equivalents tiaprost/kg), whilst the injection site retained less than 0.009% of the administered dose (no concentration given). In the other tissues examined the concentrations detected were below 0.15 \( \mu \)g equivalents tiaprost/kg. At 3 days post administration, levels could only be detected in the kidneys (0.29 \( \mu \)g equivalents tiaprost/kg).
Conclusions and recommendation

Having considered that:

- tiaprost is used in individual animals for infrequent and non-regular treatment,
- treated animals are unlikely to be sent for slaughter immediately after treatment,
- the substance is extensively metabolised and rapidly excreted,
- by 24 hours after treatment, the maximum amount of total residues which might be ingested from pig or cattle meat (excluding the injection site) and cows milk amounts to less than 3.75% of the ADI for tiaprost;

the Committee concludes that there is no need to establish an MRL for tiaprost and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

<table>
<thead>
<tr>
<th>Pharmacologically active substance(s)</th>
<th>Animal species</th>
<th>Other provisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiaprost</td>
<td>Bovine, porcine, ovine, equidae</td>
<td></td>
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</tbody>
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