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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

KETOPROFEN

SUMMARY REPORT

1. Ketoprofen, 2-(phenyl 3-benzoyl) propionic acid, is a non-steroidal anti-inflammatory drug belonging to the arylpropionic acid group and was synthesised in 1967. It was introduced into human medicine in France and Great Britain in 1973.

2. In veterinary medicine, it is indicated :

· in the treatment of inflammatory and painful conditions of the bones and joints and muscular-skeletal systems in cattle, horses, dogs and cats;

· in the symptomatic treatment of colic in horses and cattle, at dose-rates of 2 or 3 mg/kg (injectable route).

3. Ketoprofen inhibits the biosynthesis of PGE2 and PGF2 alpha without affecting the ratio of PGE2/PGF2 alpha.

4. Ketoprofen administered by intravenous or intramuscular routes to cattle and horses is well tolerated up to 5 times the recommended dose for periods 2 or 3 times longer than those used for treatment.

5. Single dose toxicity studies were conducted using oral and parenteral routes. In mice, rabbits and dogs, the LD_{50} by all routes (oral, subcutaneous, intraperitoneal) was approximately 500 mg/kg bw. In rats, results were more variable from 30 to 480 mg/kg bw. Clinical signs reported were those usually observed with other NSAIDs.

6. Out of the 9 repeat-dose studies in various species, a NOEL could be established in three 1 month-studies (rat feeding study - 6 mg/kg bw/day; rat oral - 2 mg/kg bw/day; dog oral - 2 mg/kg bw/day but only 2 animals were used in this study) and in one 6-month oral study carried out in baboons (4.5 mg/kg bw/day).

7. In fertility studies, in rats, effects of ketoprofen on male and female reproduction functions were observed with a NOEL of 3 mg/kg/day.

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8. After oral administration, no embryotoxic or teratogenic effects could be seen in rats and mice. However, in rats, ketoprofen was maternotoxic at 9 mg/kg bw/day. In rabbits, ketoprofen was maternotoxic for doses higher than 2 mg/kg bw/day after oral administration. The NOEL for embryotoxicity was 2 mg/kg bw/day.

9. In a set of mutagenic tests (Ames, Test CHO/HGPRT, Chromosome aberration test in CHO, Micronucleus Test) ketoprofen and its metabolite RP 69400 (Ames, Micronucleus Test) did not show mutagenic activity.

10. The two carcinogenicity studies carried out in mice (4, 8, 16 or 32 mg of ketoprofen for 105 consecutive weeks) and on rats (3, 4.5 and 7 mg of ketoprofen for 91 weeks followed by a 13-week observation period) showed no treatment-related effects on the incidence or distribution of spontaneous tumour profile of the strain of animals used.

11. The toxicological NOEL of 2 mg/kg bw, derived from the results of the teratogenicity toxicity study in rabbits would lead to a toxicological ADI of 0-0.020 mg/kg bw per day (i.e. 1.2 mg per person per day) after applying a safety factor of 100.

12. In humans, somnolence and dizziness were observed in 8.7% of patients treated at 100 mg/adult (vs. 5.7% in placebo group). A single oral administration of 6.25 mg of ketoprofen per adult showed a slight analgesic effect.

13. As the duration of the pharmacological effect observed after oral administration of 6.25 mg per adult is limited (4 hours), as the plasma life of ketoprofen in humans is short (1.5 to 3 hours), a pharmacological NOEL of 3 mg per day, corresponding to half of the dose inducing a slight pharmacological effect, may be extrapolated from the human data provided. So, applying a safety factor of 10, a pharmacological ADI of 0.005 mg/kg bw, i.e. 0.3 mg per day per person can be established.

14. The pharmacological activity of RP 69400 was between 10 and 100 times less than the parent compound one's.

15. Ketoprofen is converted into a carbonyl-reduced derivative, the RP 69400 (2-(phenyl 3-alpha-hydroxybenzoyl) propionic acid). The metabolite RP 69400 was found in significant amounts in plasma of all species except the rat where only trace levels were detected.

    Ketoprofen is strongly bound to proteins (97% in cattle). After single intramuscular administration of 3 mg of ketoprofen/kg bw supplemented with ^{14}C ketoprofen, plasma data showed a good relationship between total radioactivity and the sum of ketoprofen and RP 69400.

16. Ketoprofen represents about 50% of total activity from 4 to 8 hours post treatment.

In cattle after intramuscular administration, ketoprofen is rapidly absorbed ($t_{1/2}$ ka = 0.15-0.25 h). Bioavailability ranged from 85% to 100%. After a single intramuscular administration of 3 mg of ketoprofen/kg bw (with 14C methyl-ketoprofen), 90% of the radioactivity was recovered in the urine within 96 hours: 90-93% of the radioactivity was due to the metabolite RP 69400, whereas ketoprofen only represented 1%. The hydroxyl derivatives in position 3 and 4 represented only 0.5 to 2.7% of the urine metabolites. About 6% of the administered dose was recovered in the faeces.

17. After a single intramuscular administration of 3 mg/kg bw. of ^{14}C-ketoprofen to calves, the ratio ketoprofen/total residue could be evaluated: 56% for muscle, 35% for fat, 2% for liver and 56% for kidney. At the injection site, the ratio was close to 85%.

18. In horses, after intravenous administration of 2.2 mg of ketoprofen/kg bw/day, ketoprofen and RP 69400 were no longer detected in plasma three hours after injection. In urine, concentrations of metabolite RP 69400 (free and conjugated forms) were lower than those of ketoprofen. Metabolites 3- and 4- hydroxy-ketoprofen could not be detected either in plasma or in urine.

19. In cattle, after a single intramuscular administration of 3 mg/kg bw with ^{14}C ketoprofen, only trace levels were detected at the injection sites, 96 hours after treatment. After repeated administrations of 3 mg/kg bw/day/3 days, ketoprofen and RP 69400 could only be measured in kidneys, 24 hours after the third injection: 0.19 ± 0.14 µg/g for ketoprofen and 0.24 ± 0.17 µ/g for RP 69400. In other tissues, they were either non detectable (< 0.025 µg/g for ketoprofen and 0.05 µg/g for metabolite RP 69400) or lower than the quantification limit (0.05 µg/g for ketoprofen, 0.1 µg/g for RP 69400). At the injection site, corresponding to the 3rd injection, only ketoprofen was detectable, the mean concentration being 1.51 ± 1.68 µg/g.

20. Ketoprofen and its metabolite RP 69400 could not be detected (<0.025 µg/ml) in the milk at any milking both during and after treatment by ketoprofen at the recommended dosage.

21. No residue depletion study was carried out in the horse. However, from the comparison of basic pharmacokinetic parameters obtained for cattle and horses, it can be concluded that tissue depletion of ketoprofen in horse will be faster than in cattle.

22. There is an adequate and transferable analytical HPLC method with UV detection technique to ensure the monitoring of ketoprofen residues in the various tissues of cattle and in muscle of horses. The limits of detection and of quantification of this method are 25 and 50 µg/kg respectively.

Having considered that:

- In liver, fat and muscle, no residue of ketoprofen could be detected at 24 hours after the end of the treatment;
- In milk, no residue of ketoprofen could be detected during or after the treatment;

Having also considered the criteria laid down by the Committee for inclusion of substances into Annex II of Council Regulation (EEC) No 2377/90, and in particular that:

- ketoprofen is used in a small number of individual animals and for infrequent and non-regular treatment;
- the animals are unlikely to be sent for slaughter immediately after treatment;
- ketoprofen is rapidly and extensively detoxified and excreted.

The Committee considers that this substance does not present any risk for the consumer and recommends the inclusion into Annex II of Council Regulation (EEC) No 2377/90 of ketoprofen in accordance with the following table :

Pharmacologically active substance(s)	Animal species	Other provisions
Ketoprofen	Equidae Bovine	

Furthermore, as only trace levels of residues are detected at the injection site 96 hours after treatment, the Committee recommends a withdrawal period of 4 days for edible tissues.