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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

KETOPROFEN (extension to pigs)

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 pigs for its anti-inflammatory, analgesic and antipyretic activities in case of respiratory infections and Mastitis-Metritis-Agalactia syndrome in the sow. The recommended dose-rate is 3 mg/kg bw as a single intramuscular injection.

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

4. Single dose toxicity studies were conducted using oral and parenteral routes. In mice, rabbits and dogs, the LD_{50} by all routes (orally, 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.

5. 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 study - 2 mg/kg bw/day; dog oral study - 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).

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

7. After oral administration, no embrytoxic 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.

8. 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.

9. 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.

10. 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/day (i.e. 1.2 mg per person per day) after applying a safety factor of 100.

11. 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.

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12. As the duration of the pharmacological effect observed after oral administration of 6.25 mg per adult is limited (4 hours), and 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.

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

14. 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). The reduction of ketoprofen into metabolite RP 69400 was demonstrated by an in vitro metabolism study of ^{14}C-ketoprofen by the microsomal and cytosol fractions of pig liver. However, this reduction is about two-fold lower than that in bovine species.

15. In pigs, after a single intravenous administration of 3 mg/kg bw, Ketoprofen is poorly distributed, the steady-state volume of distribution (Vdss) being low (= 0.17 ± 0.02 l/kg). The mean residence time (MRT) was 2.32 ± 0.41 h.

16. Thirty minutes after a single intramuscular injection of 3 mg/kg bw of ^{14}C-ketoprofen to pigs, a peak mean plasma concentration of 12.74 ± 2.50 mg equivalent ^{14}C-ketoprofen/l was observed. The concentrations decreased rapidly to reach 0.07 ± 0.01 mg equivalent ^{14}C-ketoprofen/l twenty-four hours later. For later collecting points, ^{14}C-Ketoprofen was detected as traces.

    It was shown that about 84 % of the plasma radioactivity was due to the parental compound, 7 % to RP 69400. The remaining radioactivity was due to polar materials non identified accounting to about 8 % of radioactivity.

17. In pigs, a balance study after a single intramuscular injection of 3mg/kg bw of ^{14}C-ketoprofen showed that 72 % of the total radioactivity administered were excreted via urine within 96 hours, a majority being excreted within 24 hours. Only 20 % were recovered in faeces.

    In urine, about 30 % of the radioactivity were due to RP 69400, 12 % to the parental compound, *circa* 45 % to polar components.

18. A radiometric depletion study was carried out in pigs with ^{14}C-ketoprofen at the recommended intramuscular dosage of 3 mg/kg bw :

    · Three hours post injection, the concentrations were the following : kidney (11.63 mg equivalent-ketoprofen/kg), liver (3.02 mg equivalent ketoprofen/kg), at the injection site (12.40 mg equivalent ketoprofen/kg). In the samples of skin plus fat and in muscle, the amounts were close to 1 and 0.5 mg equivalent ketoprofen/kg;

    · Twenty four hours post dose, the radioactivity levels had already decreased to 2.07 mg equivalent ketoprofen/kg in kidney and to 0.24 mg equivalent ketoprofen/kg in liver. In other edible tissues, the concentrations were close to the limit of quantification (0.03 and 0.09 mg equivalent ketoprofen/kg for muscle and skin plus fat respectively;

    · Ninety six hours post dose, ^{14}C-ketoprofen could only be measured in kidney (0.82 mg equivalent ketoprofen/kg) and in liver (0.07 mg equivalent Ketoprofen/kg).

19. In a non radiometric study carried out with 3 x 3 mg/kg bw at 12 hours apart, the concentrations of ketoprofen in the liver, muscle and skin-fat, were below the limits of quantification (0.050 mg/kg) in all animals except one in which the levels in the skin-fat and muscle were 0.058 and 0.060 mg/kg respectively, twenty-four hours after the end of the treatment. In kidney, the levels ranged from 0.067 to 0.097 mg/kg in 3 pigs and for the 4th animal, the concentration was below the limit of quantification (0.050 mg/kg). Twenty-four hours post dosing, the ketoprofen levels at the injection sites ranged fom 20.80 to 0.40 mg/kg.

    Four and ten days after the final injection, the concentrations of ketoprofen were below the limits of quantification of the method (0.050 mg/kg) for all the tissues, the injection site included.

    The metabolite RP 69400 concentrations were below the limit of quantification of 0.1 mg/kg in all tissues, at all times and in all animals.

20. Due to very fast elimination of the radioactivity, the ratio of ketoprofen/total residues and RP 69400/total residues could only been evaluated only on samples collected 3 hours after a single intramuscular administration of 3 mg/kg bw of ^{14}C-ketoprofen to pig.

    The percentage of ketoprofen residues with respect to total residues were as follows : 31.5 % for kidney, 0.3 % for liver, 72 % for fat, 94 % at the injection site.

    For RP 69400, the figures were respectively : 29 % for kidney, 78 % for liver, 10% for fat, and 3 % at the injection site.

21. An analytical method for residues detection in skin plus fat, liver and kidney of pigs has been validated according to the recommendations of Volume VI and described according to the format ISO 78/2. The limits of quantification for ketoprofen and RP 69400 were 0.050 and 0.100 mg/kg respectively. The limits of detection ranged between 0.017 to 0.031 mg/kg for ketoprofen and from 0.027 to 0.066 mg/kg for RP69400.

Conclusions and recommendation

Having 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;
- at 24 hours post-treatment, the consumer intake of residues represents approximetely 30% of the pharmacological ADI.

The Committee considers that ketoprofen does not present any risk for the consumer and recommends that its current entry into Annex II of Council Regulation (EEC) No 2377/90 should be extended to pigs in accordance with the following table :

Pharmacologically active substance(s)	Animal species	Other provisions
Ketoprofen	Porcine	

Furthermore, as 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.