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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

VEDAPROFEN

SUMMARY REPORT (2)

1. Vedaprofen is a non-steroidal anti-inflammatory drug (NSAID) belonging to the group of arylpropionic acids. It contains an asymmetric carbon, and is therefore a racemic mixture of a (+) and a (-) enantiomer. Both enantiomers contribute to the biological and therapeutic actions of vedaprofen. Vedaprofen has anti-inflammatory, anti-pyretic and analgesic properties, based on inhibition of prostaglandin synthesis. The main side effect of vedaprofen is its ulcerogenic activity. In the target animal, horse, vedaprofen (as a gel for oral use) is indicated for control of inflammation and relief of pain associated with musculo-skeletal disorders and trauma, and soft tissue lesions, at a dose of 2 mg/kg bw, followed by 1 mg/kg bw every 12 hours for up to 14 days.

2. Absorption of vedaprofen in the final gel formulation after single and multiple oral administration is rapid (maximal plasma levels are reached within 2 hours after administration) and almost complete (bioavailability is 80-90%). Vedaprofen is highly bound to plasma proteins (≥99%). The elimination half-life in plasma is 350-500 minutes. Multiple dose kinetics show that steady state is reached quickly after onset of treatment and that no accumulation occurs. Kinetics appear to be dose linear in the dose range of 1 to 2 mg/kg bw.

   Phase I-biotransformation of vedaprofen does not occur in the aromatic part of the molecule but mainly in the cyclohexane ring. The principal compound in plasma is the parent compound, followed by metabolite VII (a monohydroxylated derivative). In urine almost no parent compound is present, whereas the most abundant metabolite is metabolite VII.

   Urinary excretion accounts for approximately 70% of the administered dose, and faecal excretion for 10-14%. All metabolites are 2.5-20 times less active than vedaprofen, as judged by inhibition of thromboxane B2 formation. The most abundant metabolite VII is more than 20 times less active than vedaprofen.

3. Vedaprofen has moderate acute toxicity when administered orally to rats (LD_{50} 222-317 mg/kg bw) and mice (LD_{50} 401-519 mg/kg bw). Intra- and epidermal administration of vedaprofen to guinea-pigs did not reveal allergenic properties.

4. Repeated dose toxicity studies and tolerance studies (13-weeks study in the rat, 13-weeks in miniature pigs, 3-weeks in rabbits, 4-21 days in dogs, 13-week in dogs) reveal that, just like other NSAIDs, the main toxic effects of vedaprofen are gastro-intestinal (ulcers in stomach and digestive tract/peritonitis. Other toxic effects are a decrease in body weight and food intake, regenerative hypochromic anaemia and leucocytosis, biochemical disorders, effects on spleen, thymus, liver and kidney. All effects can probably be attributed to the pharmacodynamic activity of vedaprofen, prostaglandin synthesis inhibition. For vedaprofen an oral NOEL of 0.125 mg/kg bw/day can be established from the 13-week dog study.

5. No tolerance studies with horses were available at the time of the first evaluation. However, twice the recommended dose during the maximum treatment period in a reproduction safety study with pregnant mares did not reveal side-effects.

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6. Several studies were performed to study the effects of vedaprofen on fertility, reproduction, embryo-/foetotoxicity and teratogenicity (rat/rabbit/dog/horse). In these studies only maternal toxicity was observed (decrease in bodyweight, food intake and faecal output, splenomegaly, mesenteric lymph node hypertrophy), with a NOEL of 5 mg/kg bw/day. No 2-generation reproduction study was performed. Since, in the studies performed, vedaprofen showed no effect on fertility, was not embryotoxic or teratogenic and is used only for non-regular treatment of individual animals, a 2-generation reproduction study is not deemed necessary. Chemically related non-steroidal anti-inflammatory drugs (NSAIDs) have no effect on reproduction.

   Because vedaprofen inhibits the activity and synthesis of $PGF_{2\alpha}$, which plays an important role during parturition, vedaprofen treatment should be discontinued just before the time of parturition.

7. Vedaprofen showed no mutagenic potential *in vitro* (negative in gene mutation tests in bacteria and mammalian cells, and in a chromosomal aberration test in mammalian cells) and *in vivo* (negative in micronucleus test). Chronic toxicity/carcinogenicity studies have not been performed with vedaprofen. These are not deemed necessary because vedaprofen does not belong to a class of drugs which is known to be carcinogenic, and because mutagenicity and toxicity studies have not revealed any suspect signs.

8. As vedaprofen was initially developed for human use, pharmacokinetic and tolerance studies have been performed in healthy volunteers. Maximal plasma levels are reached within 2 hours after administration and elimination from plasma is rapid, with a half-life of 2-3 hours. No accumulation in plasma occurs after repeated oral administration of 100 and 200 mg vedaprofen, and general tolerance is good apart from upper abdominal discomfort (particularly at the high dose).

9. Four clinical studies with human volunteers were supplied additionally. They show that vedaprofen at effective dosages is badly tolerated. Even at doses that are not effective, adverse effects are noted (NOEL 50 mg per person). Due to the low number of subjects and the insufficient quality of the data these studies cannot be used to establish an ADI.

10. Based on the overall NOEL of 0.125 mg/kg bw/day found in the 13-week dog study, and a safety factor of 100, a toxicological ADI of 1.25 µg/kg bw (equivalent with 75 µg/day for a 60 kg person) can be established for vedaprofen.

11. After oral administration of vedaprofen gel (final formulation) to horses at the intended clinical dosage regimen, vedaprofen could be detected in liver (mean concentrations of 112, 44 and 24 µg/kg after withdrawal times of 4, 8 and 12 days, respectively) and kidney (1918, 488 and 265 µg/kg at 4, 8 and 12 days, respectively), but not in muscle (LOQ: 50 µg/kg) and fat (LOQ: 20 µg/kg). Metabolites of vedaprofen were only observed in liver and kidney at 4 days withdrawal in very small amounts.

12. The proposed HPLC/fluorescence method for the determination of vedaprofen in horse tissues (with LOQs of 50 µg/kg in muscle, liver and kidney and 20 µg/kg in fat) can be used in monitoring the final MRLs. The method is described in conformity with ISO 78/2, and is fully validated.

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Conclusions and recommendation

- having set an ADI of 1.25 µg/kg bw (75 µg/day/person);
- having checked the availability of a validated analytical method for residues monitoring purposes;

the Committee recommends the inclusion of vedaprofen into Annex I of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Vedaprofen	Vedaprofen	Equidae	1000 µg/kg 100 µg/kg 50 µg/kg 20 µg/kg	Kidney Liver Muscle Fat	

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