European Medicines Agency
Veterinary Medicines and Inspections

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

FIROCOXIB

SUMMARY REPORT

1. Firocoxib (3- cyclopropymethoxy-5,5-dimethyl-4-[4-(methyl sulfonyl) phenyl]-2-(5H)-furanone; CAS No. 189954-96-9) is a non-steroidal anti-inflammatory drug (NSAID) that reduces prostaglandin biosynthesis through the selective inhibition of cyclooxygenase-2 (COX-2). In veterinary medicine, firocoxib is indicated for use in controlling the clinical signs of pain and inflammation associated with osteoarthritis in the dog, it is intended for use in horses for the same indications. The intended therapeutic dose in horses is 0.1 mg/kg bw/day orally for up to 14 consecutive days. Firocoxib may also be administered by the intravenous route to horses at a dose rate of 0.08 mg/kg bw/day for two consecutive days followed by oral administration for up to 14 days.

   Firocoxib is not used in human medicine.

2. The pharmacological activity of firocoxib has been studied in a number of experimental *in vitro* and *in vivo* models. Firocoxib has potent anti-inflammatory, antipyretic and analgesic properties in a number of animal species. Firocoxib is a preferential COX-2 inhibitor, displaying 350-fold selectivity for the COX-2 isoenzyme in the dog compared to the COX-1 equivalent. Firocoxib was a weak inhibitor of human COX-1 in microsomal preparations of U-937 cells. A dose rate of 4 to 8 mg firocoxib/kg bw was effective in improving the peak vertical force and weight-bearing capacity of dogs in an experimental model of urate crystal-induced synovitis. Dose rates of 0.75 to 3.0 mg firocoxib/kg bw exhibited marked antipyretic activity in the cat. The inhibitory dose 50 values for the percent change in paw swelling on days 5 and 21 in models of adjuvant-induced arthritis in the rat were estimated to be 0.35 and 0.4 mg firocoxib/kg bw/day, respectively. In a similar model, the radiographic changes in adjuvant-injected paws of rats receiving firocoxib at 1 mg/kg bw or 3 mg/kg bw were significantly less than those observed in control rats. In a GLP compliant study, firocoxib was administered intravenously at 0, 3, 10 and 30 mg/kg in rabbits. No significant effects were noted in heart rate. The respiratory rate was slightly elevated immediately after dosing in one animal in the 10 mg/kg dose group and in two animals dosed with 30 mg/kg. Arterial blood pressure was slightly to moderately decreased after dosing in all animals in the 10 and 30 mg/kg dose groups. These decreases mostly returned to baseline levels within 15 minutes after dosing. Both the respiratory and arterial blood pressure responses were judged as a transient bolus dose effect of firocoxib in the presence of anaesthesia in rabbits.

3. The pharmacokinetic profile of firocoxib has been studied in the rat, dog and horse. Firocoxib is highly protein bound in all animal species investigated. ^{14}C-Firocoxib was rapidly absorbed in the rat following the administration of a single oral dose of 30 or 100 mg/kg bw; t_{max} occurred at 4 to 8 hours after treatment. The elimination half life ($t_{½}$) for total radioactive residues was 12.2 to 14.2 hours in the rat. Most radioactivity was excreted in urine and faeces within the first 48 hours after treatment. Parent compound and two major metabolites were isolated in faeces by HPLC methodology; only trace amounts of parent compound were found in urine with two major metabolites accounting for most of the radioactivity. The major metabolites in faeces and urine were decyclopropylmethylfirocoxib and the glucuronide conjugate of this latter metabolite.

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Firocoxib was administered on a single occasion by the oral and intravenous routes at a dose rate of 5 mg/kg bw to 8 beagles (4 male; 4 female). T_{max} following oral treatment occurred at 1.25 hours. Large inter-animal variation was evident for AUC (range from 2.19 to 9.42 µg/h/ml; mean equal to 5.03 ± 2.58 µg/h/ml), C_{max} (range from 0.24 to 0.92 µg/ml; mean equal to 0.52 ± 0.22 µg/ml) and oral bioavailability (range from 16.6 to 78.7%; mean equal to 36.9 ± 20.4%). In a repeat dose kinetic study in the dog (*n* equal to 8), ^{14}C-firocoxib (60 mg/kg bw) was administered once daily orally for 7 consecutive days. Peak radioactivity was obtained approximately 2 to 4 hours after administration of each dose. Steady state was achieved within 3 days. By 72 hours after treatment with a final dose, radioactivity in all tissues sampled were approaching or below background levels, with the exception of bile which contained approximately 17 µg equivalents/g. The major metabolic pathways for firocoxib in the dog were similar to those observed in the rat.

The pharmacokinetics of firocoxib in the horse were investigated in a GLP-compliant study in which 0.1 mg firocoxib/kg bw was administered once by the oral or intravenous routes. Mean C_{max} was 0.075 and 0.21 µg/ml following treatment by the oral and intravenous routes, respectively. Firocoxib declined bi-phasically following intravenous administration, with an elimination half-life ($t_{1/2}$) of 34 hours. After oral administration, firocoxib was rapidly absorbed with a T_{max} of 4 hours. Firocoxib concentrations subsequently decreased exponentially in parallel with those following intravenous administration; the elimination $t_{1/2}$ was 30 hours. The mean AUC (0-∞) was 2.32 and 2.98 µg/h/ml for the oral and intravenous routes, respectively. The mean clearance value was 49.8 and 36.7 ml/h/kg for the oral and intravenous routes, respectively. Mean plasma concentrations of firocoxib were not quantifiable 72 hours after oral administration and 96 hours after intravenous administration (limit of quantification equal to 0.0075 and 0.025 µg/ml for 2 and 1 ml plasma samples, respectively). The absolute oral bioavailability of firocoxib in the horse was 79%. Following oral administration, firocoxib disposition in the horse was linear within the dose range 0.05 to 0.20 mg/kg bw.

In a second GLP-compliant study, firocoxib was administered by the oral route to horses at a dose rate of 0.1 mg/kg bw for 14 consecutive days. Plasma concentrations of firocoxib reached steady-state after the 8th daily dose and declined to the limit of quantification (0.0075 µg/ml) by 14 days after last dose. The kinetics of firocoxib were linear following 14 daily doses with mono-exponential decay. Inter-subject variability was low. The AUC based over the course of one complete treatment interval at steady-state concentration was 0.145 µg/day/ml. The elimination half life ($t_{1/2}$) was 2.14 days, the clearance was 689 ml/day/kg and the volume of distribution was 2130 ml/kg. Residues of firocoxib in plasma above the limit of quantification were detectable for between
7 and 14 days.

^{14}C-Firocoxib was administered orally to horses (*n* equal to 10) at a dose rate of 0.3 mg/kg bw daily for 7 consecutive days. Total radioactive residues in plasma were usually 25 to 50% higher than the corresponding plasma concentration of firocoxib. The elimination half life ($t_{1/2}$) was 64.5 hours and steady-state concentration was achieved after approximately four days. Unchanged parent compound was the major fraction present in faeces and most tissues. Six radiolabeled fractions were detected in urine including parent compound (less than 6% of the total radioactive residues, a decyclopropylmethylated metabolite and a glucuronide conjugate of this metabolite. Another major metabolite more than 10% of the total radioactive residues in urine was not definitively identified. The glucuronide conjugate of decyclopropylmethylfirocoxib was also a significant fraction detected in faeces.

4. The acute oral LD_{50} value for firocoxib was more than 2000 mg/kg bw in the rat and in the mouse. The acute dermal LD_{50} value was more than 2000 mg/kg bw in the rabbit. There were no signs of systemic toxicity evident in these acute studies.

5. Two GLP-compliant repeat dose oral toxicity studies were performed in the rat. In the first dose range-finding study, daily doses of 0, 50, 150 or 500 mg firocoxib/kg bw/day were administered by gavage for 2 weeks. Food consumption was decreased over the first three days of treatment at 500 mg/kg bw/day (both sexes) and 150 mg/kg bw/day (males only). Despite an initial decline at the highest dose tested, body weights were comparable between groups over the entire course of the study. Albumin concentrations and the albumin:globulin ratio were significantly reduced at the 500 mg/kg bw/day dose level. Necropsy findings at 500 mg/kg/day bw that were significant

included decreased cardiac weights and increased incidences of hepatocyte vacuolation, renal tubular cell vacuolation and follicular cell hypertrophy in the thyroid gland. At 150 mg/kg bw/day, the incidence and severity of the hepatic, cardiac and thyroid changes were markedly reduced. Due to the presence of a low incidence of cage staining and mild hepatic changes at the lowest dose tested, a NOEL could not be retained from this study.

In the second study, firocoxib was administered orally by gavage to groups of rats (n equal to 20 per group) at dose rates of 0, 3, 10, 30 and 60 mg/kg bw daily for 3 months. Salivation was seen sporadically throughout the study period in some rats of both sexes receiving dose rates more than or equal to 30 mg/kg bw. Although there were 3 premature decedents in this study, a clear dose-response relationship was not evident. There was a transient, though significant increase in food consumption and body weight gain in female rats at all dose levels tested. Female rats receiving 60 mg/kg bw also exhibited a significant reduction in body weight during the 4-week recovery period. Although numerous changes were evident on haematology and biochemistry (decreased serum urea and bilirubin concentrations; increased cholesterol and total protein concentrations), many of these changes were of low magnitude and dubious biological significance as mean values usually fell within historical control ranges and a clear dose-response relationship was sometimes absent. No gross changes considered to be test article-related were noted at post-mortem examination. Histopathological examination revealed increased liver weights (with centrilobular hepatocyte hypertrophy) and hypertrophy of thyroid follicular cells at dose rates equal or more than 30 mg/kg bw. Many of the hepatic and thyroid changes were reversible after the 4-week recovery period, except for the increase in liver weights in high-dose females. Increased liver weights and centrilobular hypertrophy of hepatocytes was also detected in females at the 10 mg/kg bw dose level. The histological changes noted in the liver and thyroid glands were considered to represent an adaptive response to treatment with a microsomal enzyme inducer. A significant increase in kidney weights was evident in all treated groups. Although an increased incidence of basophilic tubules was sporadically observed in some treated rats, no consistent pattern of microscopic lesions accompanied this latter finding. Due to the presence of significant organ weight changes (kidney) at all dose levels tested, a NOEL could not be retained from this study.

6. Firocoxib was tested in a series of GLP-compliant tolerance studies conducted in the dog. The target organs for toxicity in the dog include liver, brain and gastrointestinal tract. Gastrointestinal tract pathology affecting the mucosa was evident especially when firocoxib was administered at dose rates of more than or equal to 15 mg/kg bw. Firocoxib displayed enhanced toxicity when administered to dogs below 3 months of age. Effects on lipid metabolism were noted at 5 mg/kg bw/day in one study. Brain vacuolation was detected in dogs receiving dose levels of more than or equal to 15 mg/kg bw/day. However, these vacuoles were not accompanied by any reactive gliosis or inflammatory cell infiltrate. Mild glossal/pharyngeal lesions were recorded in treated animals in a number of studies. Whilst 5 mg/kg bw was generally well tolerated in most studies, dose rates of more than or equal to 15 mg/kg bw were usually associated with adverse side-effects.

7. A GLP-compliant tolerance study was conducted in the target species in which firocoxib was administered orally to groups of horses (6 animals/group) at dose levels of 0.1, 0.3 or 0.5 mg/kg bw/day for 30 days (representing 1, 3 and 5 times the recommended therapeutic dose). Oral lesions were present in all test groups (including controls) and no dose-response relationship was evident. Although erosive/ulcerative lesions were also observed elsewhere in the alimentary tract, there was no significant increase in the treated groups. Whilst the post-treatment heart rate was significantly reduced at the 0.1 mg/kg bw/day dose level, this was not considered biologically significant. Mean body weight was significantly increased in the 0.5 mg/kg bw/day treatment group.

   Although a wide variety of clinical chemistry parameters were significantly altered compared to controls decreased bilirubin, increased urea, increased triglycerides, increased chloride and decreased hepatic enzymes), most of these changes were of relatively small magnitude and dubious biological significance. Reductions in blood glucose and calcium concentrations were noted in some treated groups, but a clear dose-response relationship was lacking. A decrease in the total protein and globulin fractions was evident at the highest dose tested. Although an increased tapeworm burden was recorded in the caecum of the same group at post mortem examination, there was no significant increase in the incidence of nematode-related lesions within

the intestinal wall of treated horses. Treatment at the 0.5 mg/kg bw dose level was associated with a significant reduction in various Red Blood Cell parameters. Alterations in differential White Blood Cell percentages were also noted, but once again, were considered of dubious biological significance. Incidental gross lesions and microscopic lesions were found at post mortem examination in all animals from all groups, including controls. None of the lesions were considered to be treatment related. Firocoxib treatment did not significantly alter the liver weight to terminal body weight ratio at any dose level tested.

8. A GLP-compliant one-generation reproductive toxicity study was conducted in the rat with firocoxib. In this study, firocoxib was administered at dose rates of 0, 1, 3, 30, 300 and 600 mg/kg/day to male and female Sprague-Dawley rats (26 males and at least 23 sperm-positive females/group). Males were treated for 10 weeks prior to mating and continually through the 3-week mating period (i.e. at least 13 weeks in total). Females were treated for at least 2 weeks prior to mating, during the entire gestation period and for a minimum of 3-6 weeks post parturition (i.e. at least 11 weeks in total). Occasional deaths were reported at the time of parturition or shortly thereafter (1, 2, 4 and 3 females in the 3, 30, 300 and 600 mg/kg bw groups, respectively). Feed consumption was significantly increased at various time points in males at dose rates equal to or more than 30 mg/kg bw. Treatment-related reductions in maternal feed consumption were noted throughout lactation in the mid, mid-high and high dose groups. Early in the lactation period, the reduction in feed consumption was solely associated with maternal toxicity, while the significantly lower consumption seen on post-natal days 7 to 14 and 14 to 21 was associated with maternal and developmental toxicity. In females, gestation body weight and/or body weight gain were reduced towards the end of gestation at dose levels equal to or more than 30 mg/kg bw. During lactation, body weight was reduced in the 300 and 600 mg/kg bw groups on post-natal days 4 and 7. In addition, total body weight gain was reduced during lactation days 0 to 4 at dose rates equal to or more than 3 mg/kg. No statistically significant differences were detected in mating performance. The percentage of successful pregnancies was significantly decreased in the 300 and 600 mg/kg bw groups. Successful deliveries were 100% (control), 96% (1 mg/kg), 92% (3 mg/kg), 100% (30 mg/kg), 76% (300 mg/kg) and 64% (600 mg/kg). The length of gestation was significantly delayed across all treatment groups compared to controls. A reduction in pup weight was seen in the 600 mg/kg bw group, while increased weights were observed in the 1, 3 and 30 mg/kg bw groups (most likely associated with smaller litter sizes in the 1 and 3 mg/kg bw groups and reduced survival in the 30 mg/kg bw group). Pup survival was significantly decreased in all treated groups. Alterations in percent survival at the 1 and 3 mg/kg bw dose levels were principally associated with deaths occurring on postnatal day 0. This adverse effect of treatment on pup viability was more marked in male progeny. Malformed tails were noted in 2 pups in separate litters in the 1 mg/kg bw dose group (2 out of 249) and one 3 mg/kg bw dose group pup (1 out of 261). The NOEL for maternal toxicity was 1 mg/kg bw, due to the effects on gestation length, pup viability and the presence of malformed tails. A traditional NOEL for reproductive toxicity was not established for firocoxib because there were pharmacodynamic and pharmacotoxic effects noted at the lowest dose tested (1 mg/kg bw) in the one generation rat reproduction study. An alternative approach, the Benchmark Dose (BMD) method was used as a quantitative, more precise method for determining a point-of-departure (POD) based on the one-generation rat study. Using an 1% Extra Risk Benchmark Dose (BMD) to account for uncertainty and variability within the study, a more conservative BMDL (lower Benchmark Dose confidence limit), applying an unconstrained model (Weibull model) was calculated to be 0.043 mg/kg/day.

   A two-generation reproductive toxicity study was not available, however taking into account the Note for guidance on the establishment of maximum residue limits for minor animal species (EMEA/CVMP/152a/97-FINAL) and considering that the substance is intended for use in horses only which is considered a minor species, such study was not required.

9. A series of GLP-compliant developmental toxicity studies were conducted with firocoxib in the rat and the rabbit. In the rat, an initial dose range-finding study was performed in Sprague-Dawley rats at dose rates of 1, 3, 10, 30 and 300 mg/kg bw. A transient reduction in food consumption and body weight gain was noted in high-dose group dams over gestation days 3 to 6. No significant increase in gross pathological abnormalities was noted in any of the treated dams. No statistically significant differences in uterine weights were detected between firocoxib treated dams and controls. Although average litter weights were similar across all groups, foetal

weights from treated groups were slightly lower than controls. Two foetuses were malformed. One foetus in the mid-high dose group had a gross external malformation (imperforate anus and thread-like tail); one foetus in the high dose group had a heart vessel malformation involving no aortic arch, no innominate vessel and no subclavian vessel. Whilst 30 mg/kg bw can be retained as a provisional NOEL for maternal toxicity (no histopathological data), no such value can be retained for foetotoxicity due to the lack of statistical analysis of the foetal data obtained.

A definitive oral developmental toxicity study was performed in Sprague-Dawley rats (24 to 27 pregnant dams/group) at dose rates of 0, 3, 300 or 1000 mg/kg bw between gestation days 6 to 19. A significant reduction in maternal feed consumption was noted at dose rates more than or equal to 300 mg/kg bw. Maternal body weights and uterine weights were also reduced at the highest dose tested. However, when body weights and body weight gains were corrected for uterine weights, no significant differences were observed between treated dams and controls. Foetal weights of the high dose group were significantly reduced compared to controls. The number of live foetuses was significantly lower in the high dose group with corresponding increases in the number of resorptions and deaths. Foetal survival parameters were similar between control, low and mid dose groups. There was a reduction in the male to female progeny ratio with increasing firocoxib dosage. One mid dose foetus was malformed (tail abnormally long with an imperforate anus), while 49 foetuses in the high dose group had gross external, cephalic, visceral or skeletal malformations. Gross external abnormalities consisted of threadlike, kinked, stubbed, absent or vestigial tails (plus imperforate anus), stub body, arthogyroposis (forelimbs) and clubbed limbs. Visceral malformations occurring at dose rates more than or equal to 300 mg/kg bw included malformed greater vessels of the heart, absent kidneys, rectal dilation and hydronephrosis. The number of foetuses without any skeletal variations was 44.2% in the low dose group, 36.7% in the control group, 27.7% in the mid dose group and 1.8% in the high dose group. Skeletal anomalies at dose rates more than or equal to 300 mg/kg bw included absent ribs/vertebrae, reduced or bent bones, supernumerary ribs, anomalies of the pelvic girdle and incomplete ossification of the skull. The NOEL for developmental toxicity in this study was 3 mg/kg bw.

An initial dose range-finding study was performed in New Zealand white rabbits from days 5 to 28 of gestation at dose rates of 0, 10, 50, 100, 300 and 500 mg/kg bw. Mortality was observed at dose rates more than or equal to 50 mg/kg bw. Feed consumption and body weight/ body weight gain were significantly reduced at dose rates more than or equal to 50 mg/kg bw. Gross necropsy findings indicating gastrointestinal tract pathology were evident at dose rates more than or equal to 10 mg/kg bw. Uterine weights in the 10 mg/kg bw dose group were comparable to controls. Uteri of all other treated rabbits (50 mg/kg bw and higher) did not have any viable foetuses and as such weighed significantly less than controls. No gross external anomalies were observed in foetuses of the control or 10 mg/kg bw treated groups. Due to the low number of viable pups available for analysis, no NOEL was retained for developmental toxicity in this study.

In a second definitive teratogenicity study, firocoxib was administered to pregnant New Zealand rabbits (23 to 24 pregnant does/group) at dose rates of 0, 1, 3 and 10 mg/kg bw from days 6 to 28 of gestation. Food consumption and body weight gain were unaffected by treatment. Uterine weights were significantly reduced in the 10 mg/kg bw group. The pregnancy rate ranged from 96% to 100% according to group. The number of live implants or foetuses was significantly lower with corresponding significant increases in the number of resorptions and deaths in the 10 mg/kg bw group. Post implantation losses and resorptions were also elevated in the 3 mg/kg bw group. One control, 4 low, 12 mid and 11 high dose foetuses were malformed. Although a clear dose-response relationship was lacking, there was an increased incidence of gastrochisis in the progeny of treated dams. Visceral malformations consisted of malformed greater vessels of the heart: one foetus in the low dose group, one foetus in the mid dose group, two foetuses in the high dose group. Treatment-related skeletal anomalies were observed in the mid and high dose treated groups: fused sternebrae, abnormal ribs, fused or misaligned vertebrae and malformed bones in the limbs. A higher incidence of incomplete ossification of the pubic bone was observed at 10 mg/kg bw. Skeletal variations including incomplete ossification of the skull were seen at a higher incidence in the 1 and 3 mg/kg bw groups compared to controls, although a similar finding was absent at 10 mg/kg bw. The NOEL for maternal toxicity can be set at 3 mg/kg bw, with a NOEL of 1 mg/kg bw for foetal toxicity. Although equivocal findings were recorded at the lowest dose tested, 1 mg/kg bw can also be retained as a LOEL for developmental toxicity as the effects

noted did not exhibit a clear dose-response relationship and often occurred at an incidence within the range of historical control data.

10. A series of GLP-compliant mutagenicity studies were conducted with firocoxib. Negative results were obtained in an *in vitro* assay for gene mutation in *Salmonella typhimurium* TA98, TA100, TA1535 and TA1537 and *E.coli* (WP2uvrA) using test concentrations of 0 to 5000 µg/plate with and without metabolic activation. In an *in vitro* mammalian cell gene mutation assay using mouse lymphoma cells (L5178Y), test concentrations of 25 to 150 µg firocoxib/ml did not induce any significant increase in mutant frequencies in cloned colonies when tested in the presence and absence of metabolic activation. In a further *in vitro* mammalian cell chromosomal aberration assay, firocoxib did not induce any significant increase in structural or numerical chromosomal aberrations in Chinese Hamster Ovary cells at test concentrations of 62.5, 125, 250 and 500 µg/ml, either in the presence or absence of S_9. An *in vivo* micronucleus assay was conducted in the mouse in which firocoxib was administered by two intraperitoneal injections to groups of CD1 mice at test concentrations of 400, 800 and 1600 mg/kg bw/day. No significant increase in micronucleus induction was detected in bone marrow erythrocytes of mice dosed with firocoxib up to the maximum dose tested. The data available from this series of *in vitro* and *in vivo* studies indicate that firocoxib is not mutagenic.

11. No carcinogenicity data were submitted for firocoxib. However, it was considered that carcinogenicity studies were unnecessary in light of the absence of any structural alerts for this family of compounds, the negative mutagenicity data and the absence of any pre-neoplastic lesions in the repeat dose toxicity studies.

12. No data were provided on the potential microbiological properties of residues of firocoxib, including potential effects on the human gut flora and micro-organisms used in industrial food processing. However, taking into account the chemical properties of this compound, no such data were considered necessary.

13. No data specifically addressing the immunotoxic properties of firocoxib were provided. However, due to the absence of any structural alerts or specific concerns deriving from the repeat dose toxicity studies, no such data were deemed necessary.

14. As firocoxib is not used in human medicine, no data relating to the use of this molecule in humans were available. Data on substances belonging to the same class of cyclooxygenase-2 (COX-2) inhibitors indicating adverse cardiovascular effects in humans have been considered in conjunction with studies on firocoxib relating to target species tolerance and pharmacovigilance data. The available data do not show an increase in cardiac toxicity in animals undergoing treatment with firocoxib. By extrapolation from animals to humans, and particularly when used as a veterinary medicinal product when much humans are expected to be presented with much lower concentrations of residues, firocoxib residues are not expected to cause a cardiovascular risk to public health.

15. The presence of transient vacuolation within the brain tissue of some dogs treated at dose rates more than or equal to 15 mg/kg bw was demonstrated. As yet, the mechanism involved in the pathogenesis of this lesion remains unresolved. However, in a GLP study in mice administered firocoxib at doses of 0, 10, 30 and 100 mg/kg bw intraperitoneally, reactivity and spontaneous activity were slightly increased at the upper dose only for up to 6 hours. No other effects on awareness, coordination, reflex and autonomic nervous system function were observed. The NOEL for this study was 30 mg/kg bw.

16. A pharmacological ADI could not be established for firocoxib from the submitted data. However, it is noted that the most important pharmacodynamic effects related to the effects of firocoxib on delayed parturition, on the effect on the ductus arteriosus of the offspring and on the viability of newborn animals. This effects are recognised as including both COX-1 and COX-2 type effects. Moreover, these effects have been taken into account in establishing the benchmark dose.

17. The one-generation reproductive toxicity study in rats was considered the pivotal study to derive a toxicological ADI which led to the establishment of a BMDL of 0.043 mg/kg for pup mortality. Applying an uncertainty factor of 200, a temporary ADI of 0.215 µg/kg or 12.9 µg/person is

calculated derived from the standard factor of 100 and applying an additional factor of 2, to account for limitations in the reproductive toxicity data package.

18. In a metabolism study on 10 horses which received 7 consecutive daily doses of radiolabelled compound at a dose of 0.3 mg/kg bw and slaughtered at 0, 0.25, 3, 7, 14 and 21 days post treatment, the half-life of firocoxib was determined as 2.7 days (64.5 hours). As in other species, the primary route of metabolism of firocoxib is via decyclopropylmethylation followed by glucuronidation. The major route of excretion is the urine, accounting for 65 to 69% of total residue recovered. Faeces accounted for 16 to 18%. Excretion of firocoxib was rapid with 71 to 79% of the administered dose being recovered within 3 days of last dose. The ratio of marker to total residues was found from this study to be 85 to 93% for liver, 45 to 63% for kidney, 77 to 94% for fat and 76 to 92% for muscle. Parent compound is therefore the appropriate marker residue for tissues of horses.

19. In a joint pharmacokinetic and tissue residue study on 25 horses which received 14 consecutive daily doses of firocoxib orally at 0.1 mg/kg bodyweight and slaughtered in groups of 5 at 0, 1, 3, 7 and 14 days, residues depleted rapidly in all edible tissues. While a protocol for the conduct of the HPLC assay has been provided along with chromatograms from individual samples, very limited information was provided on the validation of the method as used in this particular study. Intra and inter-day assay results as well as the data concerning fortified samples run with test samples were not provided. The analysis of samples postdates the validation of the method by 18 months.

20. A routine analytical HPLC-method with UV detection described according to ISO standard 78/2 is available for the determination of residues of firocoxib in liver, kidney, fat and muscle of horses, with a limit of quantification of 5 µg/kg for all edible tissues. The marker residue is first recovered from equine tissues through homogenisation with acetonitrile followed by solid-phase extraction column cleanup. The range of compounds tested for specificity does not include meloxicam or tolfenamic acid. The variation in results provided on the stability of extracts in kidney and liver are not sufficient. The method is not fully validated, especially with respect to specificity and the stability of extracts.

Conclusion and recommendation

Having considered that:

- a temporary ADI of 0.215 µg/kg or 12.9 µg/person can be established,
- in any case, an extension of the MRLs to a major species will require the provision of a full safety data in accordance with Council Regulation (EEC) No 2377/90,
- firocoxib was retained as the marker residue, accounting for 89, 45, 77 and 76% respectively of total residues in liver, kidney, fat and muscle of horses,
- the limit of quantification for all edible tissues was 5 µg/kg,
- a routine analytical method is available for horses although it is not validated in accordance with Volume 8 of the Rules Governing Medicinal Products in the European Union;

the Committee for Medicinal Products for Veterinary Use recommends the inclusion of firocoxib for horses in Annex III 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
Firocoxib	Firocoxib	*Equidae*	10 µg/kg 15 µg/kg 60 µg/kg 10 µg/kg	Muscle Fat Liver Kidney	Provisional MRLs expire on 1.7.2007

Based on these MRL values, the daily intake will represent about 99% of the temporary ADI.

Before the Committee for Medicinal Products for Veterinary Use can consider the inclusion of firocoxib in Annex I of Council Regulation (EEC) No 2377/90, the points included in the list of questions should be addressed.

LIST OF QUESTIONS

1. The analytical method should be validated with respect to selectivity versus meloxicam and tolfenamic acid.
2. Further stability testing of extracts in kidney and in liver over a reasonable period of time should be provided by the applicant.