SCIENTIFIC DISCUSSION

I. SUMMARY OF THE DOSSIER

Previcox tablets are uncoated, round chewable tablets manufactured in 57 mg and 227 mg strengths and half-scored to facilitate treatment of dogs of variable bodyweight. The tablets contain firocoxib as the active substance, which is a non-steroidal anti-inflammatory drug (NSAID) belonging to the Coxib group, which acts by selective inhibition of cyclooxygenase-2 (COX-2).

Previcox is intended for the relief of pain and inflammation associated with osteoarthritis in dogs over 10 weeks of age or weighing more than 3 kg. The recommended dose is 5 mg per kg bodyweight once daily. Side–effects such as emesis and diarrhoea have occasionally been reported. These reactions are generally of a transitory nature and are reversible when the treatment is stopped.

In January 2007, CVMP agreed to authorise an extension application to Previcox. The intended indication in horses is the alleviation of pain and inflammation in animals with ortheoarthritis and reduction of associated lameness. The intended therapeutic dose in horses is 0.1 mg firocoxib/kg bw/day orally for up to 14 consecutive days. Previcox 0.82% oral paste for horses is presented in pre-filled oral syringes containing 7.32 g of oral paste labelled in 100-kg dosing increments. Each syringe contains sufficient product to treat a 600 kg horse.

Data relating to maximum residue limits of firocoxib have been previously reviewed by the CVMP as part of an MRL application. Based on those data, firocoxib has been included in Annex III of Council Regulation 2377/90. The proposed withdrawal period for meat and offal (horse) is 26 days.

II. QUALITY ASSESSMENT

Composition

Previcox tablets are uncoated, round chewable tablets containing either 57 mg or 227 mg of firocoxib as active substance. Conventional pharmaceutical excipients for tablets are used. Iron oxides (E172) are used to provide tablet colouring and flavouring agents are also added.

Previcox 0.82% oral paste for horses is presented in pre-filled oral syringes containing 7.32 g of oral paste labelled in 100-kg dosing increments. Conventional pharmaceutical excipients (colourant, adsorbant, thickener, viscosity modifier and vehicle) are used and full details are included in the SPC.

Container

The tablets are packaged in blisters composed of clear PVC film with a paper-backed-aluminium foil. The paper backed aluminium foil is heat-sealed onto the PVC layer. Both the heat-seal coating and the PVC layer are in contact with the product and both comply with Directives 90/128/EEC and 2002/72/EC for food contact materials. Packaging specifications including reference IR spectra and certificates of analysis were provided for both clear and opaque blisters, however the final product will be marketed only in clear blister packs for each strength.

The oral paste for horses is presented in a white polypropylene syringe barrel with a white low density polyethylene cap, a thermoplastic rubber rod tip, and a white polypropylene plunger rod which includes a white or coloured polypropylene stop ring. Each syringe contains a net weight of 7.32 g of oral paste and is labelled in 100-kg dosing increments. Each syringe is packaged in an individual carton box. Specifications from the dosage form manufacturer are provided for each component. Diagrammatic and dimensional specifications of the containers are provided, as are typical IR spectra for the syringe, cap and rod tip.

Clinical trial formula(e)

Initial developmental studies for the tablets were carried out on formulations containing 20 % firocoxib. Based on these studies a preliminary formulation was derived and used for initial dose-

ranging and efficacy studies. This formulation had only minor differences to the final composition and these minor changes would not be expected to result in variations in terms of bioavailability or pharmacokinetics. Pilot scale batches of each strength of the proposed formulation were used for the pivotal safety and efficacy studies.

Safety and dose determination trials for the oral paste for horses used formulations very similar to the final formulation but with active substance content varying. The differences in formulations used in some clinical trials are described in detail in the dossier. The final formulation selected was used for safety and efficacy clinical trials.

Development Pharmaceutics

Tablets

During the course of product development, two polymorphic forms of the active substance were discovered. Form A is a metastable polymorph while form B is a stable monotropic form. During manufacture of the active substance form B is consistently produced. Particle size of form B can vary (and it is insoluble in water), and the effect of this parameter on bioavailability was investigated. The relationship between particle size, flow characteristics and dissolution profile was investigated and an appropriate particle size specification for the active substance was set.

Compatibility studies established that the active substance is compatible with commonly used excipients. Both wet granulation and direct compression methods of manufacture were investigated.

Details of palatability studies used to select a suitable flavouring agent for the tablets are included in the dossier. Various combinations of iron oxides were evaluated for their ability to produce a tablet of the desired tan/brown colour. The product is described as a chewable tablet. The formulation is considered chewable by virtue of its palatability and relatively rapid disintegration.

The particle size range of the excipients was also evaluated and excipients may be blended, milled or sieved prior to inclusion in the formulation.

Various equipment was evaluated on scale up and the critical parameters in the process identified. Content uniformity results for full and half tablets show that the process is robust. Uniformity of weight, dissolution, disintegration and assay results also demonstrate the quality of the tablets produced by the process.

Development studies in the proposed packaging showed no difference between samples protected and unprotected from light.

Oral Paste

Early formulations contained varying active substance concentrations. The final active substance concentration was chosen with reference to the dose (0.1 mg/kg) and convenience of administration to horses up to 600 kg bodyweight in plastic syringes. The active substance is poorly soluble in water and the vehicle was chosen because of its ability to solubilise firocoxib. Because the active substance is dissolved in the vehicle, particle size and polymorphic properties of the active substance are not relevant to the bioavailability of the formulation. In order to produce a semi solid formulation, several viscosity modifying agents, were investigated. Good paste viscosity (with penetrometer) was achieved with the final formulation. Various development studies were carried out in order to optimise the formulation, to ensure satisfactory penetration value, minimise liquid separation and optimise the concentration of other components. Because the formulation does not include an antimicrobial preservative, the product was tested for antimicrobial effectiveness. The microbiological quality of the proposed paste formulation according to Ph.Eur. 2.6.12/2.6.13 was demonstrated.

The plunger rod of the syringe is calibrated with increment markings at 100 kg, 200 kg, 300 kg, 400kg, 500 kg and 600 kg. Deliverable mass was determined at each of the increment markings to demonstrate that the syringe will consistently deliver the desired mass of product across the dose range. Studies carried out to demonstrate compatibility of the product and packaging were confirmed during long term and accelerated stability studies. The syringe components are widely used for this

type of dosage form. The formulation was optimised in conjunction with syringe design to deliver 0.1 mg of active per kg bodyweight, with each 100 kg increment on the syringe delivering 1.22 g of paste.

Method of Manufacture

Tablets
The manufacturing formula for the proposed batch size was presented. A minimum and maximum batch size were defined. The manufacturing process consists of sequential addition and blending of the excipients and the active substance followed by direct compression into the desired tablet weight.

The final blend is compressed into 57 or 227 mg tablets and packaged in clear PVC-foil blisters. In-process results for all physical parameters for both tablet strengths demonstrate that all in-process specifications are met. Physical controls (hardness, thickness, weight uniformity, friability) during compression are also detailed and appropriate limits set. Compliance with the finished product specification was demonstrated. Satisfactory process validation data and a validation protocol were presented.

Oral Paste
The manufacturing formula for the proposed batch size was presented. The manufacturing process, flow chart and in-process controls are described in detail in the dossier. The process is straightforward, involving dissolution of the active substance and the excipients in the vehicle. In-process results (mixing times, temperature, ejectable content) demonstrate that the proposed overfill volume and in-process limits are appropriate to ensure a deliverable weight of not less than the declared amount.

Satisfactory process validation data demonstrate the processes to be reliable and robust. A validation protocol for the commercial batches was presented.

Control of Starting Materials

Active substance

Firocoxib inhibits cyclooxygenase (COX) or prostaglandin H-synthase (PGHS) isoform 2 to produce its anti-inflammatory activity. The active substance is not detailed in any pharmacopoeia and a specification was provided which includes tests for appearance, identity, particle size, purity, residual solvents and impurities. Specified and unspecified impurities will only be reported if present at levels greater than 0.1 %.

Firocoxib exists in two polymorphic forms, form A and form B. During manufacture of the active substance form B is produced. Flow charts of each stage of the manufacture of the active substance are provided as well as detailed descriptions of the manufacturing processes. Adequate specifications for all raw materials used in the process are provided.

Structural characterisation of firocoxib (NMR ^{1}H, NMR^{13}C, MS and IR) is provided along with a detailed physico-chemical characterisation.

The final active substance is tested to the specification provided, which is in-line with general pharmacopoeial principles and the impurity limits comply with VICH-CVMP guidelines for a new drug substance. All specified impurities are limited in the final specification. Limits for all related substances are below the qualification threshold detailed for impurities in VICH-CVMP guidelines. Residual solvents (either Class 2 or Class 3 solvents) used in the synthesis of firocoxib are limited as per VICH-CVMP guidelines.

Stress testing as part of the stability testing of the active substance demonstrates that no degradation products are formed during testing of the active substance in its solid form. The active substance is not sensitive to either heat or light. Firocoxib is packaged in LDPE double bags and cardboard or fibreboard drums. Confirmation was provided that the stability data presented for the active substance were generated on milled active substance. Polymorphism, microbiological quality, colour and clarity

remain unchanged for the duration of the stability studies. A retest period of 24 months for the active substance was agreed and this is supported by the data presented.

Batch data provided are in compliance with the proposed specification and demonstrate that material of the proposed specification is routinely produced. Levels of unspecified impurities are not detailed as the specification states that levels will only be reported if present above VICH-CVMP guidelines.

The only change made to the documentation presented for the active substance for the oral paste for horses presentation is the removal of the specification for particle size.

Excipients

Tablets
Conventional pharmaceutical excipients are used and specifications and certificates of analysis in compliance with current monographs are provided for all of the excipients listed in a pharmacopoeia. Both iron oxides are included in Directive 94/26/EC.

Two flavouring agents are included in the formulation and neither is included in a pharmacopoeial monograph. Specifications provided are based on those detailed in the Food Chemical Codex and/or compliance with Directive 88/388/EEC for flavours has been shown. Typical certificates of analysis for the flavouring agents used, demonstrating compliance were provided. Specifications and certification provided are considered sufficient to control the quality of the materials.

Oral paste
Conventional pharmaceutical excipients are used and they all comply with the relevant Ph.Eur. monograph.Typical certificates of analysis are presented for each excipient.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Certification is provided by the manufacturer that the synthesis of the active substance is entirely chemical and that no materials of animal origin are used, either directly or indirectly, in the process. The tablet formulations comply with the current TSE-Risk assessment according to Commission Directive 1999/104/EC and Note for Guidance EMEA/410/01-Rev. 2.

A declaration is provided stating that all the components used in the manufacture of Previcox oral paste for horses comply with Directive 1999/104/EC and the current TSE guideline (EMEA/410/01-Rev. 2). All components of the product are of chemical, vegetable or synthetic origin. Declarations are provided from the active substance manufacturer and the supplier of triacetin (because of the presence of glycerol in this excipient).

Control tests on the finished product

Tablets
Specifications and details of routine tests for control of the finished product including appearance, identity, assay, related substances, content uniformity (including half tablets), tablet mass and dissolution were provided. Disintegration, friability, water content and microbiological quality were also determined for some lots. All tests were suitably validated.

Related substance limits are in line with VICH-CVMP guidelines with respect to reporting levels. Individual degradation products are limited to below the identification and qualification limits. All residual solvents are controlled within VICH option 1 limits.

The only excipients present in the formulation requiring identification are the iron oxides. Identification is confirmed by compliance with an identification test in USP for ferric oxides.

Certificates of analysis for all batch analysis data, from the dosage form manufacturing site, have been provided and were acceptable.

Oral paste
Specifications and details of routine tests for control of Previcox oral paste finished product including appearance, identity of the active, assay, related substances, content uniformity, density, penetration value, identification of the colourant and microbiological purity were provided. Skip testing of microbiological quality is acceptable given the non-aqueous nature of the formulation and the data presented to date.

Details of all test procedures and analytical methods (suitably validated) were provided. The HPLC assay/related substances and the TLC identification methods have been satisfactorily validated in line with VICH requirements. The tests and methods described in the release specification are considered suitable to control the quality of the finished product. Batch analysis data were presented which support the validity of the manufacturing method and the robustness of the formulation. Further batch data on full scale batches manufactured at the manufacturing site tested according to the approved specifications will be provided at the time of commercial manufacture.

Stability tests on the Finished Product

Tablets
Stability studies were conducted in both clear and opaque blisters however, the difference in the PVC layer (clear versus opaque) is not considered significant as the active substance is not photo-labile in the solid state and in both cases PVC is the contact material. Hardness and divisibility of the tablets are unaffected by storage.

Stability data were provided and were considered acceptable to support the proposed shelf life of 36 months with no specific storage conditions for both the clear and opaque blister packs. The product will be marketed only in clear blister packs. Microbiological quality was carried out on batches packaged in clear blisters and complied with Ph.Eur. limits. Based on additional data submitted post-authorisation it was agreed to add a storage condition of 'Do not store above 30°C' for both strengths of tablets.

No decrease in active substance content or increase in impurities is observed. Total impurities remain below 0.1 %. Dissolution after 30 minutes largely remains above 90 %. The stability studies provided support a shelf-life of the finished product of 3 years.

Oral paste
Stability studies were carried out on three batches, filled into primary containers and stored under various conditions. Samples were stored under VICH long term (25°C/60%RH), intermediate (30°C/60% RH) and accelerated (40°C/75% RH) storage conditions. Studies were also carried out to investigate the effect of exposure to light and temperature cycling. Under long term, intermediate and accelerated storage conditions no significant change in active substance content is observed. Microbiological quality was determined following storage for 12 months at 30°C/60%RH and confirms that the product does not support microbiological growth.

In the VICH light effect and temperature cycles studies no significant changes in any of the tested parameters are observed. The stability data presented demonstrates that the product is extremely stable at all storage conditions. No significant change in any of the parameters tested is observed. The increase in water content noted is minimal, even under accelerated conditions and the absence of a limit for water content on the shelf life specification was considered acceptable. A shelf life of 3 years with no special precautions for storage was approved.

In-use Stability Tests

Tablets

Given that the use of half tablets is detailed in the SPC, half tablets of both strengths have been demonstrated to be stable for up to 7 days when stored at 25°C/60%RH. Water content was monitored and no significant changes observed. Any part-used tablets should be discarded after 7 days.

Oral paste

An in-use study was carried out on two batches. Paste was expelled up to the 200 kg increment and samples were stored for 3 months at the intermediate temperature of 30°C/60%RH. No microbiological testing was carried out during the in-use study. All results remain within specification. An in-use shelf life of 3 months is supported by the data provided.

Overall Conclusion on Quality

The data provided are satisfactory and adhere to current guidelines. Details of the manufacturing process are provided which show that product of the desired quality is consistently produced for both the tablet and oral paste formulations. Firocoxib is an active substance not detailed in a pharmacopoeia and suitable tests and specifications to routinely control the quality of the active substance produced were provided. The stability studies support a shelf-life of three years for the tablets and an in-use shelf-life of 7 days for the half tablets. The oral paste release specification is well designed to control the quality of the product, and the stability studies support the proposed shelf-life of 3 years and in-use shelf life of 3 months for that formulation.

3. SAFETY ASSESSMENT

Pharmacokinetics

Absorption

Firocoxib is rapidly absorbed with peak plasma concentrations within 1-1.5 hours after oral administration of the recommended dose. The data showed large inter animal variations with mean AUC values of 5.03 µg*h/ml; C_{max} of 0.52 µg/ml and a bioavailability of 36.9 %. A proportional relationship between plasma concentrations to actual dose administered could be demonstrated.

The average steady state concentration in plasma of dogs receiving firocoxib orally for 7 days was achieved within three days. Feeding is unlikely to impact on the bioavailability of firocoxib. An appropriate recommendation relating to administration with or without food has been included in the product literature.

Distribution

Six hours after 7-day oral administration of radiolabelled firocoxib, the highest residue concentrations were recorded in bile, stomach, large intestine and small intestine. Residues in the remaining organs, tissues and body fluids were low. Three days after the final dose, the mean concentrations of radioactivity in organs, tissues and fluids were markedly lower. No accumulation of parent compound was observed following repeated administration.

Firocoxib is extensively bound to plasma proteins (more than 90 %) and interaction with other strongly bound substances, such as other NSAIDs, anticoagulants, can be expected. An appropriate warning is therefore included in the SPC and product literature.

Metabolism

Firocoxib is extensively metabolised, predominantly by dealkylation and glucuronidation in the liver. The major metabolites were identified. The pattern of metabolites was broadly similar for male and female dogs.

Excretion

Following multiple oral administrations, elimination of parent compound and related metabolites is rapid (mean $T_{½}$ of 7.59 hours) and virtually complete 3 days after the treatment. While renal excretion is probably a route for final elimination, the primary route of excretion would appear to be through the gastrointestinal tract via bile (with a potential entero-hepatic cycle).

The pivotal pharmacokinetic data in rats, dogs and horses were submitted and assessed with the MRL application. One additional equine pharmacokinetic study was submitted for the oral paste application, which was only considered as supportive data.

In horses, firocoxib is rapidly absorbed and achieves mean peak plasma concentrations of 0.075 µg/ml within 4 hours after administration. Mean (+SD) bioavailability of firocoxib following administration of the final formulation is 79 (+31) %. The elimination half-life after a single dose is 29.6 (+7.5) hours. Following multiple oral administrations, steady state is achieved by approximately the eighth daily dose. Firocoxib is extensively metabolised. The principle metabolic pathways are dealkylation and glucuronidation. Elimination is principally in the excreta (primarily the urine) with some biliary excetion also observed. Firocoxib is strongly bound to plasma protein.

Toxicological studies

Single dose toxicity

Data on single dose toxicity were submitted and assessed with the initial application. The acute oral LD_{50} value for firocoxib was more than 2000 mg/kg bodyweight in the rat and in the mouse. The acute dermal LD_{50} value was more than 2000 mg/kg bodyweight in the rabbit. There were no signs of systemic toxicity evident in these acute studies. The data indicate that firocoxib has a low acute toxicity potential.

Repeated dose toxicity

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.

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.

Reproductive toxicity, embryotoxicity/foetotoxicity including teratogenicity

A teratogenicity study was carried out in which rats were given daily oral doses of up to 1000 mg firocoxib/kg bodyweight/day from day 6 to 19 of pregnancy. Maternal toxicity was characterised by a transient decrease in feed consumption and reduction in body weight very early in gestation (days 6 - 12) and the maternal NOEL was considered 3 mg/kg/day. Foetal mortality, alterations to growth, and structural alterations were observed in the foetuses of dams administered 1000 mg/kg/day. At 300 mg/kg/day, an increase in only structural alterations was observed and a NOEL for developmental toxicity was 3 mg/kg/day.

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. 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 and one 3 mg/kg bw dose group pup. 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 a study was not required.

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 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.

Based on data demonstrating the embryotoxic and foetotoxic potential of firocoxib in rats and in the absence of data for pregnant bitches, the Committee concluded that firocoxib should be contraindicated for use during pregnancy and lactation in dogs. In addition, a warning was included in the product literature (section 5.6 of the SPC) to indicate that maternotoxic and other developmental toxicity might occur at approximately the recommended therapeutic dose.

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 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.

Mutagenicity

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*. In an *in vitro* mammalian cell gene mutation assay using mouse lymphoma cells, 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. Based on a battery of *in vitro* and *in vivo* mutagenicity studies that complied with the relevant VICH Guideline, there is no evidence that firocoxib is likely to pose a significant mutagenic risk.

Carcinogenicity

CVMP 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.

Effects on Skin and Eyes

Firocoxib did not induce skin sensitisation by repeated dermal application in guinea pigs and there was no evidence of acute dermal irritation in rabbits. Firocoxib is not considered to be an occular irritant in rabbits.

Observations in humans

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. Although the potential adverse effects following the therapeutic use of coxib drugs in man are well known, based on the ADI and MRLs previously adopted by CVMP, residues in edible foodstuffs are not considered to pose a cardiovascular risk to public health. The potential for human toxicity relating to end users is addressed under “User Safety”.

Microbiological studies (studies on human gut flora and organisms used in food processing)

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. Taking into account the chemical properties of this compound, no such data were considered necessary.

User safety

The active substance, firocoxib is not used in human medicine and no studies have been provided on human safety. The excipients are either widely used in other pharmaceutical products or generally regarded as non-toxic. The only route of exposure that might present a hazard to humans is accidental ingestion of tablets. The Committee considered a worst-case scenario of ingestion of two 227 mg tablets by a 10 kg child (equivalent of an ingested dose of 45.4 mg firocoxib /kg).

Taking into account that firocoxib has low toxic potential following acute oral exposure, the Committee concluded that the risk to user safety with this formulation, and its method of presentation, is low and no greater than similar products on the market.

Oral paste

The user safety assessment addressed several key points relating to the use of firocoxib paste including safety profiles for the various excipients, a hazard assessment (based on the previously reviewed toxicity studies), an exposure assessment, a user risk assessment and risk management strategy.

The review of the excipients reveals most to be inert chemicals or additives commonly used in foods or pharmaceutical products. The hazard assessment reviewed the key results from the safety studies assessed above. The safety profile of firocoxib is well established, and the potential adverse effects on human health are thus somewhat predictable. The issue on risk of adverse cardiovascular effects has already been addressed in the context of the application for Firocoxib Maximum Residue Limits (EU/04/140/MER).

The user safety assessment employed referenced exposure and transfer factors, as deemed appropriate to each defined reasonable worst-case exposure scenario, to determine the level of firocoxib that is dermally or orally available rather than calculating a specific volume of formulated paste product available to the user. For the estimation of the user exposure the applicant considered as a worst case scenario the treatment of one horse per day, for up to 14 days and that the dermal absorption is 2%. The acute dermal and oral LD_{50} values were clearly well above the worst-case exposure scenario.

Data from single (acute) and repeated dose dermal toxicity and sensitisation studies in laboratory animals with firocoxib or with individual excipients in the formulation were used in the human health risk assessments provided. Even though transient topical exposure to the firocoxib paste formulation is not expected to result in skin or eye irritation or sensitisation based on the data available, it is conceptually possible that a small sub-population of individuals with sensitive skin may experience a transient reaction. Therefore, as a precautionary measure, risk management statements are included in the SPC. *Avoid contact with eyes and skin. If it occurs, rinse affected area immediately with water. Wash hands after use of the product.*

Also, given the fact that reproductive toxicity was the most sensitive toxicological endpoint, the SPC includes a warning statement concerning use of the product by women of child-bearing age.
Women of child-bearing age should avoid contact with, or wear disposable gloves, when administering the product.

Ecotoxicity

Tablets

This veterinary medicinal product is indicated for use in individual companion animals only. Based on the relevant VICH-CVMP Ecotoxicity Guideline, the Committee concluded that the use of this product does not cause any risk to the environment.

Oral paste

Phase I Assessment

A phase I assessment was provided for the oral paste for horses. This assessment took account of the pharmacodynamics of the product, its' pattern of use and the Phase I decision tree of the relevant VICH guideline. In addition, calculations were estimated for the PEC_{soil} through excretion from

pastured horses and from fertilising the land with manure from treated stabled horses. The calculations estimated the maximum PEC_{soil} following direct excretion on pasture was 11.2 µg/kg, while the corresponding value using manure from stabled horses was 1.5 µg/kg if the ground was ploughed and 7.5 µg/kg if left unploughed. Both these latter values were below the trigger value of 100 µg/kg for a Phase II assessment contained in the VICH guideline.

Conclusion on safety assessment

Firocoxib has a low acute toxicity potential following single exposure with a NOEL of 2000 mg/kg in rat and mouse (oral) and rabbit (dermal). Repeat dose toxicity studies in rats demonstrated that the target organs for toxicity were the liver, thyroid gland and kidney. Several studies in the dog indicated that firocoxib was generally well tolerated at a dose rate of 5 mg/kg bw, although multiples of this were associated with adverse effects on the liver, CNS and GI tract. Although firocoxib displays preferential activity for COX-2, significant gastrointestinal pathology may occur at high dose rates. The presence of vacuoles in the brain was detected in some of the canine studies performed. In addition, glossal/pharyngeal lesions and possible effects on lipid metabolism were detected in some studies.

Although a reproductive toxicity study was submitted, the study in question only addressed one generation, not two. Developmental toxicity studies revealed that firocoxib was embryotoxic/foetotoxic in both the rat and rabbit inducing a variety of external, visceral and skeletal malformations, anomalies and variations. The rabbit was far more sensitive than the rat to these effects. Consequently firocoxib is contraindicated for use during pregnancy and lactation in dogs.

A series of *in vitro* and *in vivo* mutagenicity studies using firocoxib yielded negative results, both in the presence and absence of metabolic activation. Although carcinogenicity data were not presented, there are no structural alerts for this family of compounds.

Firocoxib is not irritant to skin or eyes, and does not appear to be a sensitising agent.

The user safety profile of the product is considered acceptable. Firocoxib intended for use in dogs, does not cause any risk to the environment. A Phase I Environmental Impact Assessment for the oral paste for horses revealed that the levels of firocoxib residues likely to enter the environment (directly on pasture or as fertiliser) were below the trigger for a Phase II assessment in the VICH guideline.

RESIDUE ASSESSMENT

Depletion of residues

In a metabolism study on horses which received seven 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, 54 to 63 % for kidney, 99 to 100 % for fat and 95 to 99 % for muscle. Parent compound is therefore the appropriate marker residue for tissues of horses.

The pivotal residue depletion study was conducted to determine the depletion of marker residue (firocoxib) in edible tissues and plasma of horses slaughtered at 0.25, 3, 7, 14 and 21 days following 14 consecutive daily doses of firocoxib at 0.1mg/kg. The test product was 0.82% w/w paste formulation of firocoxib. Tissue and plasma residues were analysed using HPLC with UV detection. The LOD and LOQ were 1µg/kg and 5µg/kg, respectively, for all tissues. The study followed a well-defined protocol with due regard taken for randomisation in treatment and in the conduct of the study. The dose used and the duration of therapy accord with the intended use of the product. The study included animals of various ages and weights and included animals of each sex in equal number.

Residues above the Annex III MRLs were detected at Day 14 (final slaughter time point) in three of five liver samples, one of five kidney samples and two of five fat samples.

MRLs
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.

Conclusions of Firocoxib MRL Summary report CVMP/228774/2005-Final

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.

Withdrawal period
Residues above the Annex III MRLs were detected at Day 14 (final slaughter time point) in three of five liver samples, one of five kidney samples and two of five fat samples.

Based on statistical analysis of the available data, the withdrawal period was determined to be 20 days (based on depletion in liver). To compensate for extrapolation beyond the final slaughter time point, an additional 30% safety factor was included to give a proposed withdrawal period of 26 days.

The use of extrapolation in the determination of the withdrawal period was considered by CVMP to be acceptable, because of:

- fact that the EMEA provisional MRLs values of firocoxib were used for calculation the withdrawal period;
- the strong linearity of the depletion in tissues (with limited variability) through the 14 days studied in the residue study,
    - the fact that current guidance allows for extrapolation where the depletion kinetic is linear,
- the fact that a 30% safety factor has been added to the statistically determined withdrawal period of 20 days, and

the fact that the horse is considered a minor species.

Full details of the validated analytical method (reverse phase HPLC method) that quantifies firocoxib, being the parent compound as well as the marker residue, in liver, kidney, muscle and fat was

provided in the MRL application and is detailed in the published summary report. The limit of detection was determined to be 1.0 μg/kg. The limit of quantification was determined experimentally to be 5.0 μg/kg.

Conclusion on the Residue Part

The CVMP has recommended that firocoxib be placed in Annex III of Council Regulation 2377/90 with MRLs of muscle: 10 μg/kg; fat: 15 μg/kg; liver: 60 μg/kg; and, kidney: 10 μg/kg.

Based on statistical analysis of the available data, the withdrawal period was determined to be 20 days (based on depletion in liver). To compensate for extrapolation beyond the final slaughter time point, an additional 30% safety factor was included to give a withdrawal period of 26 days.

The arguments in support of extrapolation and the proposed withdrawal period of 26 days were considered by CVMP to be acceptable.

4 EFFICACY ASSESSMENT

Firocoxib 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.

Pharmacodynamics

The mode of action and pharmacodynamics of firocoxib has been reported in a number of publications. Firocoxib is a non-steroidal anti-inflammatory drug (NSAID) belonging to the Coxib group, which acts by selective inhibition of COX-2. *In vitro* studies demonstrated that firocoxib is a preferential COX-2 inhibitor (displays 350-fold selectivity for COX-2 in the dog, 55-fold selectivity for COX-2 in the cat and 222 to 643 fold selectivity for COX-2 in the horse). Firocoxib was a weak inhibitor of human COX-1 in microsomal preparations of U-937 cells. Firocoxib is a potent inhibitor of the arachidonic acid dependent production of PGE2 in the Chinese hamster ovary [COX-2] assay and has been shown to inhibit the COX activity of purified hCOX-2.

The pharmacological activity of firocoxib has been studied in a number of experimental *in vitro* and *in vivo* models. In further support of the activity of firocoxib, an *in-vitro* study was conducted to evaluate the potency and selectivity of firocoxib using a horse whole blood assay. In that study, the average IC_{50} value for clot-induced thromboxane (TXB2) production, an indicator of COX-1 activity, was 23.7 μM, whereas the average IC_{50} value for lipopolysaccharide-induced prostaglandin (PGE2) production, an indicator of COX-2 activity, was 0.0369 μM resulting in a COX-1/COX-2 IC50 ratio of 643.

Results from a range of *in-vivo* studies in a variety of animal species using different models of experimental inflammation (urate crystal-induced synovitis; lipopolysaccharide-induced pyrexia; carrageenan-induced paw oedema; adjuvant-induced arthritis) demonstrated that firocoxib has anti-inflammatory, antipyretic and analgesic properties.

In an urate crystal induced synovitis study in **dogs**, maximal inhibition of COX-2 was significantly greater for dogs treated with firocoxib (4 mg/kg, 82.3 $\pm$ 6.8 % inhibition) than for dogs treated with a positive control (53.8 $\pm$ 6.8 % inhibition).

In a lameness model in the **horse** (acute reversible forelimb lameness induced by an adjustable horse shoe), an oral dose of 0.125 mg firocoxib/kg was equipotent to phenylbutazone as an analgesic compound for musculoskeletal pain in the horse.

Firocoxib exhibited no specific binding/inhibitory activity when screened in a battery of 126 receptor binding and enzyme inhibition assays. The pharmacological activity of firocoxib has been studied in a number of experimental in vitro and in vivo models. It has been demonstrated that firocoxib is a preferential COX-2 inhibitor with potent anti-inflammatory, antipyretic and analgesic properties in a number of animal species.

Tolerance in the target animal species

Dogs

The recommended daily dose of 5 mg firocoxib per kg bodyweight is usually well tolerated in dogs as demonstrated by various safety studies continuing for up to 6 months and field studies continuing for up to 3 months. However, firocoxib has a relatively low safety margin and overdoses of 3-, 5- or 10-times the recommended therapeutic dose were associated with adverse side effects, some of them serious or fatal. The organs most affected in the dog are the liver (lipid accumulation), the brain (vacuolisation) and the duodenum (ulceration).

At the recommended daily dose, effects on lipid metabolism were possibly present in pups aged 3-4 months and hepatic lipidosis was noted in some animals in higher dose groups. The product literature (SPC section 5.9) therefore includes a relevant warning.

Adverse effects on the gastrointestinal tract such as inappetence, bodyweight loss, vomiting and ulceration in the duodenum were observed in high dose groups and appropriate warnings have been included in the product literature.

Histological lesions (vacuolisation) in the brain were detected in some animals and it was considered possible that these lesions may arise as a chronic and cumulative effect of firocoxib, following long term administration of overdoses. However, since no clinical signs of neurotoxicity were evident and lesions were not evident in certain recovery groups, the Committee also considered that vacuolation of white mater tracts might be a problem of tissue processing and not caused by the treatment. In the absence of further data, the Committee agreed to retain the warning statement in the product literature (section 5.9 of the SPC) and to review future PSURs for any evidence of neurotoxicity at field level.

Mild glossal/pharyngeal lesions were noted in animals in a number of target animal safety studies. However, since no such clinical signs were observed in the field studies, the Committee concluded that the product literature would not need a special warning on this issue.

Based on the target animal safety studies presented, it appears that the safety margin is narrower in pups (2-3 months old) compared to animals aged 6-12 months old (adverse effects observed in overdose were more severe in the younger animals). Consequently, it is advised that special care must be taken when treating animals aged less than 6 months of age. An appropriate warning has therefore been included in the product literature. Although geriatric dogs represent an important class of animals suffering from osteoarthritis processes, no specific target animal safety study in geriatric animals was provided. However, it was accepted that the profile of the animals included in the field studies reflected the target population for this product (older animals) and that the product was well tolerated in those studies when administered at the recommended treatment dose for up to 3 months.

Horses

Three well designed, GLP compliant studies, investigating the tolerance of firocoxib at 1x, 3x and 5x the recommended daily dose for up to 42 days were conducted. In addition, a fourth study was provided using doses of 2.5x, 7.5x and 12.5x the recommended daily dose over 3 months. The studies involved horses from different breeds and gender, aged 1 – 7 years. The horses were examined daily (including evaluation of oral cavity); further parameters included haematology, clinical chemistry, endoscopy of gastric mucosa and necropsy.

The target organs for toxicity in the horse include kidney, oral mucosa and skin.

Oral and/or skin lesions were evident in some animals in the target animal safety and in the field studies when the product was administered in the recommended treatment dose. Given that oral and/or skin lesions may occur when the product is administered at the recommended treatment dose and within 14 days of the start of treatment, an appropriate warning statement has been included in the SPC. While these lesions were typically mild at the recommended treatment dose, the incidence and severity of the lesions increased with increasing dose. The CVMP agreed to include the following warning in section 4.6 of the SPC: “Lesions (erosion/ulceration) of the oral mucosa and of the skin around the mouth may occasionally be observed in treated animals. Typically, these lesions are mild and resolve without treatment, but oral lesions may be associated with salivation and labial and tongue oedema.”

A treatment related nephropathy was detected at 2.5 and 3 times the recommended dose (treatment duration 92 days and 42 days, respectively). However, the lowest level that compound-related renal lesions occurred was at the 2.5 x dose level when administered for significantly longer than recommended (more than 6 times). In addition, the target animal safety studies demonstrated sufficient safety at the recommended treatment dose. The CVMP concluded therefore, that as a precaution, the product should be contraindicated for use in animals suffering from impaired renal function.

Intestinal ulceration/erosion was detected in a number of animals in high dose groups in two target animal safety studies. However, these intestinal ulcerations/erosions were associated with encysted small strongyles in control and treated horses. They were therefore considered a background finding and not related to treatment.

Dose determination

Dog
Two well designed *in vivo* studies were conducted using 0, 2.5, 5.0 (the proposed dose) or 7.5 mg fibrocoxib/kg bw, administered once orally. The model used was urate crystal synovitis, i.e. urate crystals were administered into predetermined stifle joints inducing moderate-severe lameness associated with joint inflammation/pain. The model was therefore considered relevant to the proposed indication. Efficacy was measured both objectively, using force plate gait analysis, and subjectively, using scoring systems based on clinical parameters.

The first study demonstrated a significant treatment effect with beneficial effect of the test product for up to 18 hours post treatment. Given the small number of test animals included in the study, it was notable that a significant treatment effect was detected. However, no apparent dose-dependent response was noted.

In the second study, depending on the variable analysed, the dose response to firocoxib reached a plateau between 2.5 and 5.0 mg/kg at both 14 and 18 hours after treatment. For all force plate parameters, the data for animals treated at 5.0 mg/kg was quantitatively better that the 2.5 mg/kg data. However, administration of 7.5 mg/kg was not any more effective than 5.0 mg/kg. It is notable that for lameness (mobility score), 2.5 mg/kg was as effective as 5.0 and 7.5 mg/kg. When all variables are taken into account, optimal efficacy is achieved at 5.0 mg/kg. For each variable, the difference between the 5 mg/kg group and the placebo group was significant ($p<0.05$) at each time point.

At 10 hours after treatment administration, plasma firocoxib concentrations exhibit a dose-dependent relationship. At 18 hours after administration of the test product, quantifiable residues of firocoxib were detected in plasma of most animals in the 2.5 mg/kg group, all animals in the 5.0 mg/kg group and most animals in the 7.5 mg/kg group. No adverse effects to treatment were observed during both studies.

These studies confirm that optimal efficacy is achieved at 5.0 mg/kg and that efficacy persists for up to 18 hours post treatment.

Horse
Two dose titration studies, investigating the efficacy of three different dosages of firocoxib administered daily over 7 days in horses with chronic (more than 2 weeks) lameness of at least one of the front limbs were conducted. If lame on both fore limbs, assessment was based on the most severely affected limb. Confirmation of a stable plane of lameness was based on clinical observations and force plate evaluations at two separate time points pre-treatment. Efficacy parameters involved force plate gait analysis and subjective lameness assessment.

The pivotal blinded, GCP compliant study was conducted at two sites, involving horses of various breeds aged 3-26 years. The horses received firocoxib in a slightly different formulation than the final one (2.05% w/w paste formulation), in doses of $\geq$0.05 mg/kg, $\geq$0.1 mg/kg or $\geq$0.25 mg/kg bodyweight or a placebo once daily for 7 days.

No adverse effects to treatment were observed during the study.

Based on the analysis of vertical peak force data, Firocoxib improved weight bearing when administered at a dose of 0.1 mg/kg. There was no significant difference in vertical peak force between the 0.1 mg/kg group and the 0.25 mg/kg group at any of the post-treatment time points.

In relation to the lameness evaluation, there was a decrease (improvement) in lameness scores in all groups. However, significant differences were detected between the negative control group and the combined treated groups on Day 2 only (p=0.0460) and between the control group and the 0.25 mg/kg group on Day 2 only (p=0.0260).

A second study was provided investigating the efficacy of 0.0625 mg/kg, 0.125 mg/kg or 0.25 mg/kg firocoxib administred once daily over 7 days. However, due to the study design (no negative control group; use of a different formulation than the final one without appropriate bioequivalence data) and limited evidence of efficacy of firocoxib even at the highest dose tested (0.25 mg/kg), this study was not considered supportive.

Dose confirmation

Dog

In addition to the two dose determination studies one well conducted double blind GCP-compliant dose confirmation study in dogs using the urate crystal synovitis model was conducted. The animals were treated orally either with a placebo, a single dose of the final product (5.0 mg firocoxib/kg bodyweight) or a reference product authorised in the EU for reduction of inflammation and relief of pain associated with musculo-skeletal disorders in the dog (vedaprofen or carprofen).

The model was considered appropriate since it gives rise to moderate-severe lameness due to joint pain/inflammation and is, therefore, relevant to the proposed indication. Also, treatments were administered when synovitis was established, therefore the ability of the test product to alleviate established disease was evaluated.

Efficacy of firocoxib at the proposed treatment dose was demonstrated using both objective and subjective measures of efficacy. In this study, differences in efficacy parameters between the test product and placebo were significant and the test product was demonstrated to be at least as effective as the reference products.

Horse

A GCP compliant dose confirmation study was provided, comparing the efficacy of a dose of 0.1 mg/kg firocoxib administered once daily for 7 days with a positive (4.4 mg phenylbutazone/kg bw) and a negative (placebo) control group.

The study involved horses aged 7-20 years and was conducted in a crossover design in three groups of horses, ranked by severity of lameness, with a 14-day washout period between treatments. All horses exhibited chronic lameness on at least one of the front limbs that was at a stable level of severity. If lame on both fore limbs, assessment was based on the most severely affected limb.

No adverse effects to treatment were observed during the study. Improvement of lameness score following the administration of firocoxib was detected at a single time point only (Day 2). However, the Day 2 analysis detected a significant sequence effect, indicating that the validity of this finding is questionable. Firocoxib had no effect on peak vertical force. By contrast, phenylbutazone administration resulted in a significant improvement in peak vertical force at all time points post treatment. However, the evaluation of the change in lameness scores demonstrated a statistically significant improvement within the treatment groups on Days 0, 2, and 6 for the firocoxib (0.1mg/kg) group and phenylbutazone (PBZ, 4.4mg/kg) group, but not within the placebo group. Furthermore, both firocoxib and PBZ were not statistically different from one another.

The discrepancy between force plate and clinical scoring might be attributed to the model used. Results in other studies/species indicated greater correlation with clinical scoring in acute models based on an induced lameness than in animals with long standing osteoarthritis. Taking into account the positive results from the dose confirmation and the field studies, the CVMP agreed that a dose of 0.1 mg/kg bodyweight would be effective for the proposed indication.

Field Trials-Tablets for Dog

Five separate studies were conducted relating to the use of the final formulation in dogs for the control of pain and inflammation associated with osteoarthritis under field conditions. The studies were performed in Europe (2), United States, Canada and Australia.

European Study – using firocoxib and carprofen

A multicentre, controlled, blinded randomised field study involving dogs with a mean age of about 8 years was conducted in the EU. The dogs were treated for 30 days with either firocoxib (final formulation) or carprofen (positive control). Carprofen is authorised in the EU for reduction of inflammation and relief of pain associated with musculo-skeletal disorders in the dog.

Inclusion criteria were dogs scoring at least "one" for lameness with a combined score for lameness and pain on manipulation of at least "two" and radiographic evidence of degenerative articular changes or other bony change. All subjective clinical parameters evaluated were scored. Exclusion criteria included prior treatment (within 7 days) with anti-inflammatory, anti-arthritic agents or corticosteroid treatment (within 30 days), systemic illness, pregnancy, fractures or surgery within the previous 14 days or planned elective surgery during the study period.

A marked improvement was noted in lameness and pain scores (relative to baseline) in both groups while animals were on treatment (improvement relative to baseline in 84.9% of dogs treated with firocoxib and 83.8 % of dogs treated with carprofen). Improvements in swelling and range of motion were not as dramatic but this is to be expected given the chronic nature of the disease condition in the test population.

Twenty per cent of dogs treated with firocoxib experienced at least one abnormality during the course of the study. The majority of these events were considered as not being treatment related. There was no significant difference between treatments with respect to incidence of abnormalities. NSAID typical adverse reactions in dogs receiving firocoxib or carprofen included diarrhoea, emesis and melena.

The test product was considered convenient to administer and palatable in most cases.

Limited information is available in dogs less than one year old, however long-term use in young dogs is less commonly encountered under field conditions than in mature animals. The SPC includes a contraindication for use in dogs less than 10 weeks of age and 3 kg bodyweight, and includes a statement that the recommended dose should not be exceeded.

Firocoxib was shown to be effective and well tolerated in adult dogs when administered in accordance with the recommended dosing schedule for 30 days.

United States Field Study – using firocoxib and etodolac

This field study was GCP compliant. This was conducted in the United States and involved dogs with a mean age of about 7 years. The dogs were treated for 30 days with either firocoxib (final formulation) or etodolac (positive control, which is not authorised in the EU). The efficacy evaluation was based on clinical assessment (lameness, pain on manipulation/palpation, joint swelling, range of motion) and force plate gait analysis by a veterinarian and subjective assessment by the animal owners.

An improvement in clinical efficacy parameters in firocoxib treated animals was shown. While a certain percentage of firocoxib treated dogs were considered improved based on force plate analyses, improvement based on clinical assessment/owner perception was much more convincing. In a non-inferiority comparison of treatments 87.3 % of all firocoxib treated dogs were considered "improved".

The field safety data generated in this study showed that 9.4 % of dogs treated with firocoxib experienced at least one abnormality during the course of the study. The majority of these events were

considered as not being treatment related. NSAID typical adverse reactions in dogs receiving firocoxib included diarrhoea, emesis and melena. There was no significant difference between treatments with respect to incidence of these abnormalities.

No long-term field safety data (>30 days) were available for this trial.

Australian Field Study - using firocoxib and etodolac

This was a controlled, blinded, multicentre, randomised study conducted in Australia using dogs with a mean age of 9 years. Dogs received either firocoxib at the proposed dosage or etodolac for 30 days. The inclusion/exclusion criteria and evaluation parameters for this study were the same as in the European study.

Since the reference product used in this study is not authorised in the EU, the relevance of the efficacy data in this study was considered limited. In addition, the numbers of dogs included were too small for the purposes of applying meaningful statistical analysis. However, it was noted that none of the firocoxib-treated dogs showed treatment related side effects.

Canadian Field Study - using firocoxib and carprofen

This was a controlled, blinded, multicentre, randomised study conducted in Canada using dogs with a mean age of about 6 years. Dogs received either firocoxib at the proposed dosage or carprofen for 30 days. The inclusion/exclusion criteria and evaluation parameters for this study were the same as in the European study.

The numbers of dogs included in this study were too small to apply meaningful statistical analysis. Based on the data generated, the efficacy of firocoxib would appear to be as efficacious as the reference product.

European Field Study - firocoxib and meloxicam

The second European field study, conducted in three European countries used dogs with a mean age of about 8 years. Dogs received either firocoxib at the proposed dosage or meloxicam for up to 90 days. Meloxicam is authorised in the EU. Inclusion/exclusion criteria were the same as those used in the other European study.

The primary efficacy variable was clinical improvement at study termination (Day 89$\pm$2). Secondary efficacy variables included clinical improvement at Day 14, 30 and 60 (non-inferiority of treatments performed) and individual parameters evaluated by the investigator (lameness, pain on manipulation, range of motion, joint swelling) and owners assessment of improvement. The dependant variable for analysis was the difference between post treatment and baseline (pre-treatment) investigator evaluation scores.

In terms of efficacy, the results showed no significant differences between the two treatments groups.

In terms of safety, no significant difference between treatments with respect to incidence of abnormalities was noted. Some of the abnormalities observed were considered to be treatment related, however, most had an unknown relationship to the treatment or were considered not treatment related. Gastro-intestinal side-effects were seen in some animals.

Efficacy of the test product when administered at the recommended treatment dose for up to 90 days is comparable to the reference product and the efficacy data were considered acceptable.

The tolerance of the product, when administered at the recommended treatment dose for up to 90 days, is acceptable. Notwithstanding that fact and the fact that firocoxib has been shown to be well tolerated in target animal safety studies, when administered at the recommended treatment dose to healthy dogs

for up to 6 months, the product literature includes a recommendation that long-term administration of the product should be reviewed regularly by the veterinary surgeon.

In addition, the Committee noted that no safety data relating to use in sick/debilitated animals were submitted. In the absence of such data, an appropriate warning statement has been included in the SPC.

Conclusion on the Clinical Part-Dogs

Tolerance studies in dogs indicated that firocoxib was generally well tolerated at the recommended therapeutic dose of 5 mg / kg bodyweight / day, although higher doses were associated with adverse effects on the liver, central nervous system and the gastrointestinal tract.

Although firocoxib displays preferential activity for COX-2, it is noted that severe adverse gastrointestinal effects may occur at higher repeated doses (five times the recommended dose in pups and ten times the recommended dose in mature dogs). The presence of vacuoles in the brain, lesions (ulceration) in the duodenum and possible effects of lipid metabolism were detected in some studies. Appropriate warnings have been included in the product literature.

Firocoxib was not as well tolerated in pups as in older dogs; therefore, it is advised that use of the product in very young animals requires careful monitoring. An appropriate statement has been included in the product literature (section 5.5 of the SPC).

Based on the dose confirmation study, efficacy of the test product at the proposed dosage has been demonstrated in an appropriate model of canine lameness using both objective and subjective measures of efficacy. It is noted that although the recommended dose is 5 mg/kg/day, the dosing recommendation will deliver dose rates in the range 5.0 to 10.3 mg/kg.

On the basis of two European field studies, it is accepted that administration of the product in accordance with the recommended dosing schedule for a period of up to 90 days resulted in an improvement in lameness score in dogs with established osteoarthritis. The test product was shown to be comparable to the reference products (carprofen and meloxicam, respectively).

The relevance of the efficacy data in the US study is limited, as the reference product is not authorised in the EU. However, it is accepted that an improvement in clinical efficacy parameters, relative to baseline, was observed in firocoxib treated animals. In addition, the value of the efficacy data in the Australian and Canadian studies is limited in that the reference product included in the Australian study is not authorised in the EU and both studies included relatively small numbers of test animals precluding meaningful evaluation of data.

Based on the data from all field studies conducted, firocoxib, when administered to otherwise healthy dogs for the management of osteoarthritis, appears to be well tolerated when used once daily in accordance with the recommended dosing schedule. Given the safety profile of the product in field and target animal safety studies, the duration of therapy should be dependant on the clinical response observed under the condition that such long-term administration would be under regular veterinary supervision. In addition, the SPC includes a statement that only administration up to 90 consecutive days has been tested.

Field Trials-Oral paste for Horse

Two GCP-compliant, controlled, blinded, multicenter, randomised field studies; one conducted in the USA and another one in Europe ; investigating the safety and efficacy of firocoxib in horses for the control of pain and inflammation associated with osteoarthritis were presented. The study conducted in the US involved horses aged 2 to 37 years of age from 9 different sites; the European field study involved horses from a total of 4 different sites.

Firocoxib oral paste was administered orally once daily for 14 days at a dose of 0.1 mg/kg to horses with chronic (i.e. more than four weeks) lameness attributable to osteoarthritis. The efficacy of firocoxib was compared with a positive control, either 2.2-4.4 mg phenylbutazone/kg bodyweight once daily from Day 1 to Day 14 in the US study; or in the European study 2.0 mg vedaprofen/kg once on Day 1, then 1.0 mg/kg twice daily from Day 2 to Day 14.

Horses that had received prior treatment with other anti-inflammatory / anti-arthritic agents or with corticosteroids within 7 or 30 days, respectively, as well as horses with systemic illness, infectious arthritis, pregnancy or any surgery were excluded from the trials. At enrolment, horses had to meet one of the following conditions: a) scored at least grade 3 out of 5 for lameness, or b) a lameness score of Grade 2 and a score of at least 2 for pain on manipulation/palpation, range of motion or joint swelling. Radiographic evidence (within previous 28 days) of osteoarthritis was present in at least one radiographic view. Navicular degeneration was also included provided there was evidence of prominent bony change.

During the treatment, animals were checked by their owners at least once daily for health problems. Any health problems or adverse reactions occurring during the course of the study were recorded. Veterinary clinical evaluation was conducted on each animal at three occasions; assessing the lameness, pain on manipulation/palpation, joint swelling and the range of motion. Also, blood samples for haematology and plasma/serum chemistry were collected and analysed at these occassions.

Based on the findings of the US study, it was concluded that Firocoxib was not inferior to phenylbutazone at Day 7 and Day 14, for all parameters evaluated. Similarly, in the European study, no significant differences were found between the firocoxib and the vedaprofen treatment for any of the variables.

97.9 % of firocoxib treated horses found the paste acceptable. 89.6% of the animal owners administering the firocoxib paste, found the paste convenient to administer.

The CVMP noted that firocoxib was comparable to the positive controls (phenylbutazone and vedaprofen, respectively) in demonstrating an improvement in lameness and the secondary efficacy variables. Based on the results of these studies, the CVMP concluded that Previcox oral paste administered once daily for 14 days at a dose of 0.1 mg/kg was as effective as other authorised products in the control/alleviation of pain and inflammation associated with osteoarthritis and the reduction of associated lameness in horses.

In both studies, the recommended treatment dose (0.1 mg/kg) was well tolerated when administered for a period of 14 days. The only adverse effect attributed to firocoxib treatment was a local inflammatory reaction in the mouth characterised by labial oedema, tongue oedema and salivation. An appropriate warning was therefore included in the product literature.

The majority of horses included in the field studies were older than five-years, which reflects the main target population. Since only a limited number of horses younger than 5 years was included in the trials and taking into account known differences in drug disposition and drug elimination between very young and adult animals, the Committee agreed that firocoxib should not be used in horses younger than 10 weeks. An appropriate warning/contraindication has been added to the SPC and product literature.

Conclusion on Efficacy-Horse

Dose determination studies and a dose confirmation study have been submitted in support of the recommended treatment dose of 0.1 mg firocoxib/kg bodyweight.

Two controlled, multi-centre studies were conducted (one in the US and one in Europe) to investigate the efficacy, safety and acceptability of firocoxib under field conditions when administered to horses orally once daily for 14 days at a dose of 0.1 mg/kg. Based on the findings of both field studies, it is concluded that the test product is not inferior to the reference products, phenylbutazone and

vedaprofen. The CVMP therefore concluded that Previcox oral paste administered once daily for 14 days at a dose of 0.1 mg/kg was as effective as other authorised products in the alleviation of pain and inflammation associated with osteoarthritis and the reduction of associated lameness in horses.

In both field studies, the recommended treatment dose (0.1 mg/kg) was well tolerated when administered for a period of 14 days. The only adverse effect attributed to firocoxib was a local inflammatory reaction in the mouth characterised by labial oedema, tongue oedema and salivation and an appropriate warning has been included in the SPC and product literature.

The safety of the test product when administered at the recommended treatment dose for periods in excess of 14 days has not been evaluated in the field. Therefore, 14 days is considered the maximum recommended duration of therapy.

5. BENEFIT-RISK ASSESSMENT

Previcox is a veterinary medicinal product containing the active substance firocoxib. Firocoxib is a non-steroidal anti-inflammatory drug belonging to the Coxib group. In *in vitro* canine whole blood assays, firocoxib exhibits approximately 380-fold selectivity for COX-2 over COX-1. The proposed indications for the product is for the relief of pain and inflammation associated with osteoarthritis in dogs and for the alleviation of pain and inflammation associated with osteoarthritis and reduction of associated lameness in horses.

The quality data provided are satisfactory and adhere to current guidelines. Details of the manufacturing processes for both the tablets and oral paste are provided which show that product of the desired quality is consistently produced. The stability studies support a shelf-life of three years for the tablets and an in-use shelf-life of 7 days for the half tablets. A shelf life of 3 years for the oral paste with no special precautions for storage and in-use shelf life of 3 months is considered to be adequately supported by the data provided. The finished product complies with the current TSE-Risk assessment according to Commission Directive 1999/104/EC and Note for Guidance EMEA/410/01-Rev. 2.

Firocoxib has a low acute toxicity potential. Repeat dose studies demonstrated that the target organs for toxicity were the liver, thyroid gland and kidney. Several tolerance studies conducted in the target species indicated that firocoxib was generally well tolerated at the recommended dose, although multiples of the recommended dose were associated with adverse effects on the liver, central nervous system and gastro-intestinal tract. The potential for adverse effects relating to these organs is appropriately and adequately addressed in the SPC. Firocoxib has a low safety margin in pups compared to older dogs; therefore, it is advised that use in very young animals requires careful monitoring.

Developmental toxicity studies revealed that firocoxib was embryotoxic/foetotoxic at sufficiently high dosage rates in both the rat and rabbit. However, the rabbit was far more sensitive than the rat to these latter effects. Firocoxib induced a variety of external, visceral and skeletal malformations, anomalies and variations in the developmental toxicity studies performed. A NOEL for teratogenicity could not be established in the rabbit. Consequently firocoxib is contraindicated for use during pregnancy and lactation.

Firocoxib is not considered to have any mutagenic or carcinogenic potential. Firocoxib is not irritant to skin or eyes, and does not appear to be a sensitising agent.

A User Safety assessment was provided and the user risk management procedures detailed in section 4.5 of the SPC are appropriate. A Phase I Environmental Impact Assessment for the oral paste for horses revealed that the levels of firocoxib residues likely to enter the environment (directly on pasture or as fertiliser) were below the trigger for a Phase II assessment in the VICH guideline.

A pharmacological ADI could not be established for firocoxib from the submitted data, however a temporary ADI of 0.215 μg/kg or 12.9 μg/person can be established. CVMP has recommended that firocoxib be placed in Annex III of Council Regulation 2377/90 with MRLs for muscle: 10 μg/kg; fat: 15 μg/kg; liver: 60 μg/kg; and kidney: 10 μg/kg. In the pivotal residue study, horses were treated with firocoxib as the proposed commercial formulation. The CVMP accepted a withdrawal period of 26 days which is based on available residue data. This duration is based on a statistically determined withdrawal period of 20 days plus a 30% safety factor to account for extrapolation in accordance with the note for guidance EMEA/CVMP/036/95.

Given the safety profile of the tablets for dogs in field and target animal safety studies, the Committee agreed that the duration of therapy should be dependant on the clinical response observed under the condition that such long-term administration would be under regular veterinary supervision.

The pharmacological activity of firocoxib has been studied in a number of *in vitro* and *in vivo* models. Firocoxib is a preferential COX-2 inhibitor with potent anti-inflammatory, antipyretic and analgesic properties in a number of animal species. In horses, firocoxib is rapidly absorbed and achieves mean

peak plasma concentrations within 4 hours after administration. Following multiple oral administrations, steady state is achieved approximately after 8 days of daily treatment. Firocoxib is strongly bound to plasma protein. Elimination is principally in the excreta (primarily the urine) with some biliary excretion also observed.

On the basis of two European field studies in dogs, it is accepted that administration of the chewable tablets in accordance with the recommended dosing schedule for a period of up to 90 days resulted in an improvement in lameness score in dogs with established osteoarthritis. The test product was shown to be comparable to the reference products (carprofen and meloxicam, respectively).

The safety of Previcox oral paste was studied in horses at doses up to 12.5 times the recommended dose for more than 6 times the recommended duration of use. The recommended treatment dose (0.1 mg/kg) was usually well tolerated when administered for a period of 14 days. Oral and/or skin lesions were noted in some animals in the dose determination and in the field studies when administered the recommended treatment dose. While these lesions were typically mild at the recommended treatment dose, the incidence and severity of the lesions increased with increasing dose. An appropriate warning statement was therefore included in the SPC.

The most significant side effect associated with long term use of firocoxib at elevated dose levels is nephropathy, similar to the other NSAIDs used in horses. This nephropathy was dose dependent, starting as a mild to moderate interstitial inflammation and minimal necrosis and edema of the interstitium in horses dosed at 2.5 times the recommended dose for more than 6 times the recommended duration of use. It progressed to an infrequent renal fibrosis and papillary necrosis at 5X the recommended dose for three times the recommended duration of use. Although the dosing range required to develop histologic signs of nephropathy is relatively narrow, the duration of use required for the signs to develop is considerably longer than the recommended treatment duration and occurs at an infrequent rate even then. The potential for the development of renal pathology in horses when the product is administered in overdose and a warning to avoid concurrent administration of potentially nephrotoxic drugs, was therefore included in the SPC and product literature.

The dose for firocoxib paste was selected using horses with naturally occurring lameness of chronic nature due to osteoarthritis. A dose level of 0.1 mg/kg once daily, reduced clinical lameness similar to a higher dose level of 0.25 mg/kg. Firocoxib was similar to phenylbutazone based on clinical lameness score although phenylbutazone was superior to firocoxib based on peak vertical force. In clinical field studies, with horses diagnosed with osteoarthritis, performed in the USA, compared with phenylbutazone and in Europe compared with vedaprofen, firocoxib oral paste satisfied the defined non-inferiority criteria, demonstrating that it was comparable to the control products. Based on the findings of both field studies, it is concluded that the test product is comparable to the reference products, phenylbutazone and vedaprofen. The CVMP therefore concluded that Previcox oral paste administered once daily for 14 days at a dose of 0.1 mg/kg was as effective as other authorised products in the alleviation of pain and inflammation associated with osteoarthritis and the reduction of associated lameness in horses.

Based on the data presented, the Committee for Veterinary Medicinal Products concluded that the quality, safety and efficacy of Previcox tablets for dogs were considered to be in accordance with the requirements of Council Directive 2001/82/EC and and that the subsequent extension application for the oral paste for horses was considered to be in accordance with the requirements of Council Directive 2004/28/EC, as amended. A favourable benefit-risk profile for this product was proven.