SCIENTIFIC DISCUSSION

I. SUMMARY OF THE DOSSIER

The application for EQUIOXX is submitted in accordance with Article 13c of Directive 2001/82/EC as amended (informed consent). The authorised product to which reference is made is Previcox 8.2 mg/g Oral Paste for Horses (EU/2/04/045/007) which was authorised in the European Community on 14 March 2007. The applicant (Merial) also holds the Marketing Authorisation for Previcox. A satisfactory letter of consent has been provided.

EQUIOXX contains firocoxib as active substance, a non-steroidal anti-inflammatory drug (NSAID), that reduces prostaglandin biosynthesis through the selective inhibition of cyclooxygenase-2 (COX-2). Firocoxib is not used in human medicine.

The indication in horses is the alleviation of pain and inflammation in animals with ortheoarthritis and reduction of associated lameness. The therapeutic dose is 0.1 mg firocoxib/kg bw/day orally for up to 14 consecutive days. EQUIOXX 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.

Firocoxib was initially included in Annex III of Council Regulation (EEC) No. 2377/90, following review by CVMP of data submitted as part of an MRL application. Firocoxib has now been included in Annex 1 of Council Regulation (EEC) No. 2377/90, following verification by CVMP of the analytical method. The proposed withdrawal period for meat and offal (horse) is 26 days. No withdrawal period has been established for milk and the product should not, therefore, be used in mares producing milk for human consumption.

A detailed description of the system of pharmacovigilance, was presented in Part I of the Marketing Authorisation application. Additional data were provided confirming registration with the Eudravigilance database. The pharmacovigilance system has been reviewed and found to be satisfactory.

Merial submitted an application to the EMEA on 28 October 2008 for an extension of the Community marketing authorisation for EQUIOXX in accordance with Annex II of Reg. 1084/2003 of 3 June 2003. The extension is to introduce a new pharmaceutical form, EQUIOXX 20 mg/ml solution for injection for horses. The solution for injection can be considered bioequivalent to the authorised reference product, EQUIOXX Oral Paste, when administered to horses in accordance with the proposed conditions of use. The indication is the same as for the oral paste 'Alleviation of pain and inflammation associated with osteoarthritis and reduction of associated lameness in horses'. This extension was authorised on 18 December 2009.

II. QUALITY ASSESSMENT

COMPOSITION

Oral Paste
EQUIOXX 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.

Solution for injection
EQUIOXX 20 mg/ml solution for injection is presented in 25 ml glass vials containing 2.0 %w/v firocoxib with the conventional pharmaceutical excipients macrogol 400 and glycerol formal as solvents.

CONTAINER

Oral Paste

© European Medicines Agency, 2010. Reproduction is authorised provided the source is acknowledged.

The oral paste 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.

Solution for injection
The solution for injection is presented in 25 ml Type 1 amber glass vials closed with a 20 mm chlorobutyl rubber stopper and an aluminium seal. Pack sizes include one vial or 6 vials of 25 ml in a carton box. Both the vials and rubber closure comply with the relevant Ph.Eur. requirements.

CLINICAL TRIAL FORMULA(E)

Oral Paste
Safety and dose determination trials for the oral paste for horses used formulations very similar to the final formulation but with the 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.

Solution for injection
During product development formulations using various solvent combinations were used in tolerance studies in cats, dogs and horses in order to establish the most appropriate solvent to employ in the solution for injection formulation. The formulation used in all other clinical studies is the same as that authorised.

DEVELOPMENT PHARMACEUTICS

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. Particle size and polymorphic properties of the active substance are not relevant to the bioavailability of the formulation, because the active substance is dissolved in the vehicle. 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. The product was tested for antimicrobial effectiveness because the formulation does not include an antimicrobial preservative. 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.

Solution for injection
Development focused on non-aqueous solutions. Potential solvents were selected based on good stability, non-toxicity, good solubility, low injection site reaction and low haemolytic effect. Based on tolerance studies and solubility and stability considerations, the final formulation was selected. In order to confirm the self preserving properties of the non aqueous formulation, preservative efficacy testing was conducted in line with Ph Eur 5.1.3. The method of sterilisation chosen was justified. The

packaging materials chosen are routinely used for this dosage form and offer a high degree of protection for the product. The use of amber vials and compatibility with the rubber closure have been adequately demonstrated. The number of broachings for which fragmentation and self sealing have been demonstrated is in line with the dosage regime for the product.

METHOD OF MANUFACTURE

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. Satisfactory GMP certificates issued by AFSSA are provided for the site of batch release (Mérial, Toulouse) and site of manufacture for the oral paste (Merial Saude Animal Ltda, Brazil).

Solution for injection
The manufacturing process of the solution for injection comprises of standard methods of compounding the active and excipients, filtration and aseptic filling. Validation data demonstrates that the process is capable of reproducibly producing batches of the desired quality. Appropriate in-process controls are in place.

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, 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 48 months for the active substance was agreed and this is supported by the data presented. A declaration is provided from the

site of batch release confirming that the active substance is manufactured at Lonza Ltd, Switzerland in compliance with GMP requirements.

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.

EXCIPIENTS

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.

Solution for injection
Macrogol 400 Ph.Eur. complies with the current monograph. Glycerol formal complies with an in-house monograph. The specifications provided for both excipients were deemed acceptable.

SPECIFIC MEASURES CONCERNING THE PREVENTION OF THE TRANSMISSION OF ANIMAL SPONGIFORM ENCEPHALOPATHIES

Oral Paste
A declaration is provided stating that all the components used in the manufacture of the 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).

Solution for injection
The solution for injection does not contain any material of animal origin.

CONTROL TESTS ON THE FINISHED PRODUCT

Oral Paste
Specifications and details of routine tests for control of the finished product including appearance, identity of the active, assay, related substances, content uniformity, density, penetration value, identification of the colourant, net content, total ejectable content 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.

Solution for injection
Specifications and details of routine tests for control of the finished product including appearance, clarity, colour, fill volume, specific gravity, related substances, identification and assay of the active, particulate matter and microbiological purity were provided. Details of all test procedures and analytical methods (suitably validated) were provided. Batch data demonstrates compliance with the specification.

STABILITY TESTS ON THE FINISHED PRODUCT

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 demonstrate 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.

Solution for injection
The stability studies on 6 batches demonstrate the product to be extremely stable with no indication of any adverse trends in the data. No widening of the assay or related substance limits are therefore applied during shelf life. Non-stability indicating tests are not included in the stability studies. A slight change in the specification for colour is appropriate for shelf life. In addition to routine temperature controlled stability studies, stability was studied following exposure to light (as per VICH, exposure to not less than 1.2 million Lux hours and an integrated ultraviolet light of not less than 200 Wh/m2) and following exposure to temperature cycling. Results for photostability and temperature cycling remain well within specification under all conditions studied. A shelf life of 3 years with no special precautions for storage was approved based on the data provided.

In-use Stability Tests

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.

Solution for injection
An in-use study was conducted in two batches of finished product. Appearance, colour and clarity conform to specification throughout. No decrease in active substance content was observed and the product passed both sterility and preservative efficacy testing. An in-use shelf life of 28 days with no specific storage precautions was accepted.

Overall Conclusion on Quality

The data provided within Part II are generally satisfactory and current guidelines are taken into account. Formulation development is well described and the product composition justified for both formulations. Product used in pivotal clinical studies was essentially the same formulation as that proposed for marketing. Details of the manufacturing process and process validation are provided which show that product of the desired quality can be consistently produced by the process as described for both the oral paste and solution for injection. The 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 the oral paste for horses and a shelf-life of 3 years and in-use shelf life of 28 days for the solution for injection.

3. SAFETY ASSESSMENT

Pharmacokinetics

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

Absorption
In the **horse**, a single dose of 0.1 mg firocoxib/kg bw was rapidly absorbed with a T_{max} of 4 hours and mean C_{max} was 0.075µg/ml. The horses were fed 12 hours prior to treatment and 2 hours post treatment. Oral treatment frequently resulted in a secondary peak in plasma concentration, the size of which varied markedly between individual animals. This finding may be partially related to the availability of food 2 hours post drug administration.

Distribution
Firocoxib is extensively bound to plasma protein (more than 90 %) with little difference in plasma protein binding capacity between different species (horse, dog, cat and rat).

In **horses**, a single dose of 0.1 mg firocoxib/kg bw was administered by the oral or intravenous routes (Study PRD96601). Mean C_{max} was 0.075 and 0.21 µg/ml, respectively. Following intravenous administration, firocoxib declined bi-phasically, with an elimination half-life ($t_{1/2}$) of 34 hours. After oral administration, firocoxib concentrations decreased exponentially in parallel with those following intravenous administration; the elimination $t_{1/2}$ was 30 hours. The mean clearance value was 49.8 and 36.7 ml/h/kg, for the oral and intravenous routes respectively. The reported oral clearance is Cl*F, not Cl, that is, it is not corrected for bioavailability. The mean AUC (0-∞) was 2.32 and 2.98 µg/h/ml for the oral and intravenous routes, respectively. Mean plasma concentrations of firocoxib were not quantifiable 72 hours after oral administration and 96 hours after intravenous administration (limit of quantification equal to 0.0075 and 0.025 µg/ml for 2 and 1 ml plasma samples, respectively). The absolute oral bioavailability of firocoxib in the horse was 79 %. Following oral administration, firocoxib disposition in the horse was linear within the dose range 0.05 to 0.20 mg/kg bw.

Following repeated oral administration (Study PR&D 0087701) of 0.1 mg firocoxib/kg bw for 14 consecutive days, plasma concentrations of firocoxib reached steady-state after the 8th daily dose and declined to the limit of quantification (0.0075 µg/ml) by 14 days after last dose. The kinetics of firocoxib were linear following 14 daily doses with mono-exponential decay. Inter-subject variability was low. The AUC based over the course of one complete treatment interval at steady-state was 0.145 µg/day/ml.

Metabolism
In **horses**, ^{14}C-Firocoxib was administered at a dose rate of 0.3 mg/kg bw daily for 7 consecutive days. The elimination half life ($t_{1/2}$) was estimated to be 64.5 hours and steady-state was achieved after approximately 4 days. Unchanged parent compound was the major fraction present in faeces and most tissues. Six radiolabeled fractions were detected in urine including parent compound (less than 6 % of the total radioactive residues), a decyclopropylmethylated metabolite and a glucuronide conjugate of this metabolite. Another major metabolite more than 10 % of the total radioactive residues in urine was not definitively identified as a glucuronide conjugate of the hydroxylated parent. The glucuronide conjugate of decyclopropylmethylfirocoxib was also a significant fraction detected in faeces.

Excretion
In **horses**, after repeated oral administration of 0.1 mg firocoxib/kg bw, daily for 14 consecutive days, the elimination half life ($T_{0.5}$) was 2.14 days, the clearance was 689 ml/day/kg and the volume of distribution was 2130 ml/kg. Residues of firocoxib in plasma above the limit of quantification were detectable 7 days post last dose in a multidose study.

Conclusions on pharmacokinetics

- 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 excretion also observed.
- Firocoxib is extensively bound to plasma protein.

Toxicological studies

Single dose toxicity

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

Repeat dose studies in the rat demonstrated that the target organs for toxicity were the liver, thyroid gland and kidney. Hepatic lesions were not always reversible within the time constraints of the studies conducted. Firocoxib appears to be a potent inducer of the MFO enzyme system in the liver. GI tract pathology was not a dominant feature in rodent species. However, only one traditional 90-day repeat dose study was submitted.

Reproductive toxicity, including teratogenicity

A GLP-compliant one-generation reproductive toxicity study was conducted in the rat with firocoxib. 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 this study. An alternative approach, the Benchmark Dose (BMD) method was used as a quantitative, more precise method for determining a point-of-departure (POD) based on the one-generation rat study. Using an 1% Extra Risk Benchmark Dose (BMD) to account for uncertainty and variability within the study, a more conservative BMDL (lower Benchmark Dose confidence limit), applying an unconstrained model (Weibull model) was calculated to be 0.043 mg/kg/day.

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

Embryotoxicity/foetotoxicity, including teratogenicity

A series of GLP-compliant developmental toxicity studies were conducted with firocoxib in the rat and the rabbit. Whilst 30 mg/kg bw was retained as a provisional NOEL for maternal toxicity (no histopathological data), no such value could be retained for foetotoxicity due to the lack of statistical analysis of the foetal data obtained.

A definitive oral developmental toxicity study was performed in Sprague-Dawley rats (24 to 27 pregnant dams/group) at dose rates of 0, 3, 300 or 1000 mg/kg bw between gestation days 6 to 19. The NOEL for developmental toxicity in this study was 3 mg/kg bw.

An initial dose range-finding study was performed in New Zealand white rabbits from days 5 to 28 of gestation at dose rates of 0, 10, 50, 100, 300 and 500 mg/kg bw. Due to the low number of viable pups available for analysis, no NOEL was retained for developmental toxicity in this study.

In a second definitive teratogenicity study, firocoxib was administered to pregnant New Zealand rabbits (23 to 24 pregnant does/group) at dose rates of 0, 1, 3 and 10 mg/kg bw from days 6 to 28 of gestation. The NOEL for maternal toxicity was 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 was also 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.

Conclusion on reproductive toxicity

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. 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. The product is contraindicated for use in breeding, pregnant or lactating animals.

Mutagenicity
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
No carcinogenicity data were submitted for firocoxib. CVMP previously 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 below 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 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".

Environmental Risk Assessment

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

The data indicate that firocoxib has a low acute toxicity potential. Repeat dose studies in the rat demonstrated that the target organs for toxicity were the liver, thyroid gland and kidney. However, only one traditional 90-day repeat dose study was submitted. Several studies ("Tolerance") conducted 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. 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.

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. Data relating to "Other Effects" were seriously limited. However, no significant concerns exist in relation to immunotoxicity or antimicrobial properties.

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 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.

Extension - Solution for Injection for Horses

EQUIOXX 20 mg/ml solution for injection contains firocoxib and is indicated for the alleviation of pain and inflammation associated with osteoarthritis and reduction of associated lameness in horses. The route of administration is intravenous.

This is a line extension of the 8.2 mg/g Oral Paste for horses. Based on the findings of a GLP bioequivalence study, EQUIOXX Solution for Injection, administered intravenously at a dose of 0.09 mg/kg, and EQUIOXX 8.2 mg/g Oral Paste, administered at a dose of 0.1 mg/kg, can be considered bioequivalent and, consequently, can be used interchangeably.

In support of the application, reference to toxicology studies previously submitted in support of the 8.2 mg/g Oral Paste for horses was provided. Cross reference is also made to studies submitted previously in respect of the MRL application for firocoxib in horses (EU/04/140/MER). For basic toxicological data relating to the active substance, the reader is referred to the EMEA/CVMP MRL Summary Report for Firocoxib.

It is noted that the safety warnings that appear in sections 4.3, 4.4, 4.5, 4.7 and 4.8 of the SPC, are in line with the safety warnings agreed for the reference product, Equioxx Oral Paste. This is appropriate given that bioequivalence is claimed.

A comprehensive user safety assessment was presented in support of this application. It is accepted that the user safety statements proposed for inclusion in section 4.5(ii) of the SPC satisfactorily address any potential risk posed by the active substance or the excipients. The product, if used in accordance with label instructions, does not pose an unacceptable risk to the user.

Given that the product is for individual animal treatment, it is not expected to pose a risk to the environment.

Given that the test (Equioxx Solution for Injection) and reference products (Equioxx Oral Paste) display essentially similar pharmacokinetics and the systemic exposure is the same, the withdrawal periods established for Equioxx Oral Paste (26 days) can be applied to Equioxx Solution for Injection.

RESIDUE DOCUMENTATION

Depletion of residues

In a metabolism study on horses which received 7 consecutive daily doses of radiolabelled compound at a dose of 0.3 mg/kg bw and slaughtered at 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 (6 hr post treatment), 1, 3, 7, and 14 days following 14 consecutive daily doses of firocoxib at 0.1 mg/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 1 µg/kg and 5 µg/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 MRLs were detected at Day 14 (final slaughter time point) in 3 of 5 liver samples, 1 of 5 kidney samples and 2 of 5 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 was 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

After initial evaluation of data relating to firocoxib in June 2006, the Committee for Medicinal Products for Veterinary Use recommended the provisional 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

.

Subsequently, In October 2006, after evaluation of additional data concerning the specificity and stability of the analytical method for the monitoring of residues, the CVMP confirmed the MRLs and recommended the inclusion of Firocoxib in Annex 1 of Council Regulation (EEC) No. 2377/90. No changes to the MRLs were required.

Withdrawal period

Residues above the Annex III MRLs were detected at Day 14 (final slaughter time point) in 3 of 5 liver samples, 1 of 5 kidney samples and 2 of 5 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 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:

- the fact that the MRLs for 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 were provided in the MRL application and are 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. The EMEA in accordance with Article 32 of Regulation (EC) No 726/2004 requested the Community Reference Laboratory (BVL in Germany) to verify the analytical method for firocoxib. CVMP discussed the report provided by BVL. CVMP reaffirmed its previous opinion that the method is suitable for residue analysis. However, it was noted that the BVL report indicated that the method was not considered to be a confirmatory or screening method in accordance with 2002/657/EC, the Directive which applies to residue control.

Conclusion on the Residue Part

The CVMP recommended that firocoxib be placed in Annex I of Council Regulation (EEC) No. 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 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 pharmacological activity of firocoxib has been studied in a number of experimental *in vitro* and *in vivo* models. *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.

In further support of the activity of firocoxib, the Applicant presented an *in vitro* study 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 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.

Tolerance in the target species of animal

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 at 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. Although it was noted that also some untreated animals developed oral lesions, the CVMP agreed to include a 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

Two dose titration studies, investigating the efficacy of 3 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 2 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 administered 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

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 3 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

Two GCP-compliant, controlled, blinded, multicentre, randomised field studies were conducted: one 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 4 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 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 3 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 occasions.

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.

The paste was found acceptable by 97.9 % of firocoxib treated horses, whilst 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 EQUIOXX 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 5 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.

Extension - Solution for Injection for Horses

A GLP study was conducted to investigate the pharmacokinetics of the oral and intravenous formulations of firocoxib. Based on the findings of that study, CVMP concludes that the test (Equioxx Solution for Injection) and reference products (Equioxx Oral Paste) can be considered bioequivalent when administered to horses in accordance with proposed conditions of use. Consequently, it is accepted that the products will have a similar efficacy profile and can be used interchangeably.

Based on data previously submitted to CVMP in support of Equioxx Oral Paste, it is known that the main target organs for toxicity are the tongue/gingival/buccal mucosa and the kidneys. Oral lesions/ulceration associated with administration of the Oral Paste at the recommended treatment dose have been recorded. Further, renal pathology (tubulo-interstitial nephropathy) has been detected when firocoxib was administered at multiples of the recommended treatment dose. In support of the present application, a good quality GLP target animal safety study designed to investigate tolerance of the test (intravenous) formulation when administered daily for five days followed by daily administrations with the reference (oral) formulation for a further period of 9 days was presented. This treatment sequence was repeated three times resulting in a total treatment period of 42 days. The product was well tolerated: with the exception of the injection site, no treatment-related adverse effects were observed clinically for any animal at any dose level during the course of the study. Comprehensive analyses of the effects of treatment on numerous blood and urine parameters were conducted: no biologically/clinically relevant effects on clinicopathological parameters were detected at any dose level. For the high dose group (5x), the following treatment-related pathological effects were recorded: oral (tongue, gingival, buccal mucosa) ulceration; and, tubulo-interstitial nephropathy.

Based on the findings of the pivotal target animal safety study and of a number of development studies it is clear that reactions at the injection site are a potential ‘adverse’ effect of treatment. This potential adverse effect is reflected in the SPC section 4.6.

In further support of the safety of the final formulation, a limited field study was conducted. In that study, evaluation of tolerance was based on observation/measurement of a limited number of clinical parameters only. However, notwithstanding the limited nature of the study, it is accepted that the results indicate that administration of the product at a dose of 0.09 mg firocoxib/kg bodyweight displayed an acceptable level of tolerance under field conditions of use.

No clinical efficacy data provided. For Equioxx Solution for Injection, the proposed indication reflects the authorised indication for the reference product, Equioxx Oral Paste.

Conclusions on Efficacy

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 EQUIOXX 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 BALANCE

The data provided within Part II are generally satisfactory and current guidelines are taken into account. Formulation development is well described and the product composition justified. Product used in pivotal clinical studies was essentially the same formulation as that proposed for marketing. Details of the manufacturing process and process validation are provided which show that product of the desired quality can be consistently produced by the process as described. The 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.

All components of the product are of chemical, vegetable or synthetic origin. The starting materials used in the production of the final product have all been declared in compliance with the current regulatory texts related to the TSE Note for Guidance (EMEA/410/01-Rev.2) and Council Directive 2001/82/EC as amended.

The toxicological profile of the active has been adequately characterised. The available data indicate that firocoxib has a low acute toxicity potential. Repeat dose studies in the rat demonstrated that the target organs for toxicity were the liver, thyroid gland and kidney. Several studies ("Tolerance") conducted 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.

Developmental toxicity studies revealed that firocoxib was embryotoxic/foetotoxic 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.

Firocoxib is not considered to have any mutagenic or carcinogenic potential.

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 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.

Since authorisation of the reference product (Previcox Oral Paste), firocoxib has been placed in Annex I of Council Regulation (EEC) No. 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, 25 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.

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.

The product was studied in horses at 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 oedema 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 3 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. In a dose confirmation study with a small sample size, the 0.1 mg/kg dose was found to offer significant clinical benefit relative to each horse's pre-study baseline. In this study, 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 North America compared with phenylbutazone and in Europe compared with vedaprofen, firocoxib paste satisfied the defined non-inferiority criteria, demonstrating that it was comparable to the control products for improvement. 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 the test product 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.

The overall benefit risk analysis is deemed positive with a sufficiently clear and complete SPC and product literature.

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of EQUIOXX oral paste for horses were considered to be in accordance with the requirements of Council Directive 2001/82/EC, as amended.

Extension - Solution for Injection for Horses

EQUIOXX 20 mg/ml solution for injection for horses is a clear colourless solution containing 20 mg firocoxib per ml of formulated product. Glycerol formal and PEG 400 are included in the formulation. The product is presented as a pre-mixed formulation in sealed, pre-filled septum-capped vials (25 ml).

EQUIOXX Solution for Injection can be considered bioequivalent to the authorised reference product, EQUIOXX Oral Paste, when administered to horses in accordance with proposed conditions of use. Therefore, it is accepted that the products will have a similar efficacy profile and can be used interchangeably. For the Solution for Injection, the proposed indication reflects the authorised indication for the reference product: 'Alleviation of pain and inflammation associated with osteoarthritis and reduction of associated lameness in horses'. An improvement in the clinical condition of horses treated with the veterinary medicinal product for the proposed indication is expected.

The solution for injection is a new pharmaceutical form and can be used interchangeably with the oral paste allowing choice of treatment options with the same efficacy profile.

The adverse effects associated with the administration of the Solution for Injection reflect those known and reported for the Oral Paste. At the recommended treatment dose, these effects are typically characterised by mild oral lesions of limited clinical significance. However, administration in overdose for extended periods may cause renal pathology. For the Solution for Injection, deposition of solution perivascularly has the potential to cause a local reaction. Overall, the target animal safety profile is considered acceptable since the adverse reactions at the recommended treatment dose are typically transient, minor in severity, and are adequately detailed in the SPC.

The product, if used in accordance with label instructions, does not pose an unacceptable risk to the user, consumer or the environment.

Evaluation of the benefit-risk balance

The product has been shown to have a positive benefit-risk balance overall. The product has been shown to be efficacious for the indication claimed.
The formulation and manufacture of Equioxx solution for injection is well-described and the specifications set will ensure that a product of consistent quality will be produced.

It is well-tolerated by the target animals and presents a low risk for users and the environment and appropriate warnings have been included in the SPC. A sufficient withdrawal period has been set.

Conclusion

The overall benefit risk evaluation is deemed positive with a sufficiently clear and complete SPC and product literature.

Based on the CVMP's review of the data on quality, safety and efficacy, the CVMP concluded that the application for EQUIOXX 20 mg/ml solution for injection for horses for 'Alleviation of pain and inflammation associated with osteoarthritis and reduction of associated lameness in horses'

is considered to be in accordance with the requirements of Council Directive 2001/82/EC, as amended, and that the benefit-risk balance is favourable.