8 December 2016
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for EQUIOXX to add a new pharmaceutical form i.e. a 57mg oral chewable tablet (EMEA/V/C/000142/X/0015)

International non-proprietary name: firocoxib

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Product profile

Invented name:	EQUIOXX
Active Substances:	Firocoxib
Target Species:	Horses
Pharmaceutical Form:	Chewable tablet
Strength:	57 mg
Therapeutic Indication:	Alleviation of pain and inflammation associated with osteoarthritis and reduction of associated lameness in horses.
ATCvet code	QM01AH90
Pharmacotherapeutic group	Anti-inflammatory and anti-rheumatic products, non-steroids
Applicant	MERIAL

Introduction

The applicant MERIAL submitted on 26 February 2016 an application for an extension to the marketing authorisation for EQUIOXX to the European Medicines Agency (The Agency) in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I point 2(d) change or addition of a new pharmaceutical form thereof.

EQUIOXX 8.2 mg/g oral paste for horse contains firocoxib, and was authorised for use in the European Union on 25 June 2008 in accordance with Article 13c of Directive 2001/82/EC as amended (informed consent). Currently the product is also available as 20 mg/ml solution for injection for horses.

This extension application is to add a new pharmaceutical form (chewable tablets) for the existing target species (horse) and approved indication and at the approved dose. The approved indication is alleviation of pain and inflammation associated with osteoarthritis and reduction of associated lameness in horses. The route of administration is oral use.

The active substance of EQUIOXX is firocoxib, an anti-inflammatory agent NSAID. The target species is horse.

EQUIOXX chewable tablets contains 57 mg firocoxib and is presented in packs containing 10 tablets, 180 tablets, 30 tablets and 60 tablets.

The rapporteur appointed is Jeremiah Gabriel Beechinor and the co-rapporteur is Maria Azevedo Mendes.

On 8 December 2016, the CVMP adopted an opinion and CVMP assessment report.

On 9 February 2017, the European Commission adopted a Commission Decision granting the extension to the marketing authorisation for EQUIOXX.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance (DDPS V8/Date: August 2015) which fulfils the requirements of Directive 2001/82/EC. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The CVMP considers that the pharmacovigilance system as described fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Manufacture, assembly and batch release of the dosage form takes place within the European Economic Area (EEA).

The manufacturer for batch release is Merial, Toulouse, France. The site has a manufacturing authorisation by French Agency for Food, Environmental and Occupational Health & Safety (ANSES ANMV), France. GMP certification dated 14 December 2015, which confirms the date of the last inspection and shows that the site is authorised for the batch release of such veterinary dosage forms, has been provided.

A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an on-site audit by a third party.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and is in line with legal requirements.

Part 2 - Quality

Composition

EQUIOXX tablets contain 57 mg firocoxib as the active substance and the excipients lactose monohydrate, microcrystalline cellulose, chartor hickory smoke flavour, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, caramel (E150d), colloidal silicon dioxide yellow iron oxide (E172) and red iron oxide (E172). The chewable tablets for horses are round, convex, scored and engraved on one side with "M" above the score and "57" below the score.

Containers

During development the following primary packagings were tested: blisters made of clear polyvinyl chloride (PVC) film with a child resistant aluminium foil and paper backing, and blisters made of white opaque aclar/laminated PVC film with a child resistant aluminium foil and paper backing.

The containers proposed for commercialisation are push-through blisters and high density polyethylene (HDPE) bottles.

The blister is made of clear PVC and aluminium foil with heatseal coating that is equivalent to the one used during development. The PVC and the heatseal coating on the aluminium side are in contact with the product. The bottle presentation is a 30 ml HDPE bottle with a polypropylene (PP) cap containing 60 tablets. Satisfactory specifications and technical drawings are provided for the packaging materials and confirmation of compliance with relevant criteria for food contact materials and/or Ph. Eur. monographs is provided.

Development pharmaceutics

Firocoxib is known to have at least two polymorphic forms. 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 varies considerably (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 set.

Compatibility studies established that the active substance is compatible with commonly used excipients. A wet granulation process showed no advantage over the direct compression method of manufacture and direct compression was therefore chosen.

Palatability studies have not been conducted in the target species. 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 the 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.

Method of manufacture

The manufacturing formula for the proposed batch size was presented. The manufacturing process is a standard direct compression tableting process and 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 tablets and packaged in the proposed market packs. Results for all physical parameters demonstrate that all in-process specifications are met. Physical controls (hardness, thickness, weight uniformity and friability) during compression are also detailed and appropriate limits set. Compliance with the finished product specification was demonstrated. Satisfactory process validation data were presented for three commercial scale batches.

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.

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. Three starting materials which contribute significantly to the structure of firocoxib have been identified. Designation of the starting materials has been appropriately justified and appropriate specifications are provided for each starting material.

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

A specification was provided which includes tests for appearance, identity, colour and clarity of solution, water content, residual solvents, sulfated ash, heavy metals, impurities, and assay. Ph. Eur. methods are utilised for standard laboratory tests and other analytical methods have been validated in accordance with VICH GL2 Validation of analytical procedures: methodology, as appropriate. The proposed specification is in line with general pharmacopoeial principles and the impurity limits comply with VICH requirements for a new drug substance. Limits for all related substances are below the qualification threshold detailed for impurities in VICH GL10 Impurities in new veterinary drug substances. Residual solvents used in the synthesis of firocoxib are limited as per VICH GL18, Impurities: residual solvents in new veterinary medicinal products, active substances and excipients.

Batch analytical data were submitted from 3 pilot-scale batches of the final active substance and results confirm compliance with the proposed specification.

Stability data is presented for three pilot scale batches and 6 full scale batches. 60-month data is available following storage at 25 ºC/60% RH, up to 36 month data following storage at 30 °C/60% RH and 6-month data following storage at 40 ºC/75% RH. 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. Polymorphism, microbiological quality, colour and clarity remain unchanged for the duration of the stability studies. A retest period of 60 months with no specific storage precautions for the active substance was agreed and this is supported by the data presented.

Excipients

Conventional pharmaceutical excipients are used and specifications and certificates of analysis in compliance with the current monographs are provided for all of the excipients listed in a pharmacopoeia. Both iron oxides used in this product are included in the Annex of Regulation 1129/2011 establishing a union list of food additives.

Two flavouring agents are included in the formulation and neither is monographed in a pharmacopeia. Specifications provided are based on those detailed in the Food Chemical Codex and compliance with the Regulation (EC) No 1334/2008 on flavourings 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.

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

All components of the formulation except lactose and hickory smoke flavour are of non-biological origin. Lactose monohydrate is sourced from milk sourced from healthy animals in the same conditions as milk collected for human consumption. No additional documentation relating to TSE compliance is therefore required.

A component in hickory smoke flavour is of biological origin and the supplier has declared that no animal origin materials are in it. The product is in compliance with the requirements of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev 3).

Control tests on the finished product

Specifications and details of routine tests for control of the finished product including appearance (visual), identity (TLC and HPLC), assay (HPLC), related substances (HPLC), content uniformity (Ph. Eur.), tablet mass and dissolution (Ph. Eur.) were provided. Microbiological quality is included on the specification as a non-routine test. All analytical methods were suitably validated in accordance with VICH GL2 Validation of analytical procedures: methodology.

Related substances limits are in line with VICH requirements with respect to reporting levels. Individual degradation products are limited to below the VICH identification and qualification thresholds. All residual solvents are controlled according to VICH GL18.

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.

Batch analysis data, from 6 pilot scale batches and one commercial scale batch manufactured at the dosage form manufacturing site, have been provided and were acceptable. Additional parameters to those listed on the specification are detailed for these batches (disintegration, water content, friability). These are provided for information purposes only and are not proposed to be added to the specification.

Stability

The shelf life specification is the same as that at release except that assay limits are widened, microbiological quality is not included and results for identification of active substance, ferric oxides, average mass and content uniformity have been reported for information but are not part of the stability program. This is considered acceptable.

The proposed limits for active substance of 92-105% are based on statistical analysis of ranges for means of 95 and 105% release specifications with confidence intervals of 99.74%. The proposed limits are in line with the stability data and are considered acceptable. Microbiological quality was carried out on a number of batches in the stability program and its omission from the specification is considered acceptable.

Data has been provided that support a storage time of the bulk tablets before packaging. Stability studies were conducted in both clear and opaque blisters similar to those proposed for marketing and in HDPE bottles. Data from six pilot scale blend batches is provided. Batches were stored at 25 °C/60% RH and 30 °C/60% RH for 36 months and at 40 °C /75% RH for 6 months. Data from seven commercial scale batches is provided. Data is presented for batches stored at 25 °C/60% RH and at 30°C/65% RH for up to 48 months and at 40 °C/75% RH for up to 12 months. No decrease in active substance content or increase in impurities is observed. Total impurities remain within specification Dissolution after 30 minutes largely within specification Hardness and divisibility of the tablets are unaffected by storage. Microbiological quality was carried out on selected batches and complied with Ph. Eur. limits.

Photostability studies have been conducted in accordance with the VICH GL5 guideline. No degradation products, changes in active substance content or physical changes were detected in batches packaged in both clear and opaque blisters when exposed to light and no specific storage precautions relating to this aspect are therefore required.

The stability studies provided support a shelf-life of the finished product of 4 years. The inclusion of the storage precaution 'Do not store above 30 ºC' is based on trends observed in the stability data for the 227 mg tablet authorised for use in dogs. Whilst that strength tablet is not proposed for use in horses, it is considered prudent to retain the same storage precautions for this product.

Overall conclusions on quality

The data provided is satisfactory and adheres to current guidelines.

The composition and development pharmaceutics are well presented and comprehensive.

Details of the manufacturing process are provided which show that product of the desired quality is consistently produced. Data has been provided that support a storage time of the bulk tablets before packaging.

Firocoxib is an active substance not detailed in a pharmacopoeia. It exists in two polymorphic forms and during manufacture form B is produced. Detailed description of the manufacturing process is provided. Adequate specifications for all raw materials used in the process are provided. Designation of the starting materials has been appropriately justified and appropriate specifications are provided for each of them. Suitable tests and specifications to routinely control the quality of the substance produced were provided. The stability studies support a re-test period of 60 months with no specific storage precautions.

The quality of the excipients used in the product is compliant with Ph. Eur. standards and EU legislation as appropriate.

The product is in compliance with the requirements of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev 3).

Appropriate specifications to control the finished product at release and during shelf-life have been provided. Analytical methods are appropriately described and validated for their intended use.

The stability studies support a shelf-life of four years for the product when stored below 30 °C.

Part 3 – Safety

Safety documentation

Firocoxib is a non-steroid anti-inflammatory substance (NSAID) marketed for dogs under the trade name Previcox (oral tablets) and marketed for horses under the trade name EQUIOXX (oral paste and injectable solution). The purpose of the current application is to obtain an extension of the marketing authorisation of EQUIOXX to a new pharmaceutical form, a 57 mg oral tablet, at the same dose regimen as the oral paste (0.1 mg/kg) and for the same indication ("for the alleviation of pain and inflammation associated with osteoarthritis and reduction of associated lameness in the horse"). The applicant advises that this application is motivated by the fact that there is an off-label use in the field of the dog tablets in the horses. EQUIOXX 57 mg tablets for horses are the same formulation as the approved product Previcox tablets for dogs (57 mg).

During the assessment procedure, the applicant chose to restrict use of this product to animals in the weight range 450 – 600 kg bodyweight to ensure accurate (safe and effective) dosing (see Part 4).

In support of this extension, pharmacokinetic studies have been conducted to compare the bioavailability of the 57 mg tablet in the horse with the bioavailability of the oral paste to allow bridging of the safety data package of the oral paste to the tablet. In the context of a line extension and taking into account that most of the data that have already been submitted and assessed in the original marketing authorisation apply to this extension, original reports and data are not provided again.

Pharmacodynamics

No data provided.

Pharmacokinetics

For a summary of the 'bridging' pharmacokinetic studies, see Part 4.

Toxicological studies

No basic toxicology data provided.

For an overview of target animal safety, see Part 4.

User safety

A user risk assessment taking into account the use of the tablet in the context of the horse indication has been provided in accordance with the CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1). However, as advised above, EQUIOXX 57 mg tablets for horses are the same formulation as the approved product Previcox tablets for dogs (57 mg). In addition, the nature and composition of the immediate packaging proposed for EQUIOXX is the same as that currently authorised for Previcox tablets for dogs. Given the similarity with the existing authorised dog tablet product, it is expected that the risk to the user will be comparable for both products. Indeed, it could be argued that the user risk associated with the use of EQUIOXX tablets for horses will be less than the potential risk associated with Previcox tablets for dogs (in particular when the exposure scenario of greatest concern is oral exposure (ingestion by a child)) given the proposal that the 57 mg tablet only will be authorised for the horse (57 mg and 227 mg tablets are authorised for the dog), the duration of use for the horse (14 days) will typically be less than that for dogs (for the management of osteoarthritis) and, when used in horses, the product will typically be stored and used outside the home environment.

In view of the above, the user safety statements accepted for Previcox tablets for dogs are considered equally applicable to EQUIOXX tablets for horses.

Environmental risk assessment

A Phase I environmental risk assessment was provided according to current guidance VICH GL 6 on environmental impact assessment for veterinary medicinal products – Phase I (CVMP/VICH/592/98). The veterinary medicinal product will only be used to treat a small number of animals in a flock or herd.

Based on the data provided EQUIOXX 57 mg tablets for horses are not expected to pose a risk for the environment when used according to the SPC.

Residues documentation

MRLs

The MRLs of firocoxib for horses have been evaluated in accordance with Regulation (EC) No 470/2009 of the European Parliament and of the Council, and the MRLs have been published by the European Commission in the Official Journal as follows:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target Tissues	Other provisions	Therapeutic classification
Firocoxib	Firocoxib	Equidae	10 µg/kg 15 µg/kg 60 µg/kg 10 µg/kg	Muscle Fat Liver Kidney	NO ENTRY	Anti-inflammatory agents / Nonsteroidal anti-inflammatory agents

All excipients listed in section 6.1 of the SPC, with the exception of chartor hickory smoke flavour, are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product. 'Chartor Hickory Smoke Flavour' consists of an aqueous solution of smoke flavour adsorbed on yeast. This solution of smoke flavour is authorised by Regulation (EU) No 1321/2013. Based on the information presented, the CVMP accepts that 'Chartor Hickory Smoke Flavour' does not possess pharmacodynamic activity at the dose at which it will be administered to the target animal, and agrees that no MRLs are required for this ingredient.

Residue studies

No residue data specific to tablet formulation have been provided. Two bioavailability studies have been conducted to compare the rate and extent of firocoxib absorption in the horse after administration as an oral paste or as a 57 mg tablet. The acceptable relative bioavailability of the tablet demonstrated in the pivotal bioequivalence study allows bridging the outcome of the residue study performed with the oral paste to the 57 mg tablet.

For a summary of the 'bridging' pharmacokinetic studies, see Part 4.

Withdrawal periods

Given that bioequivalence is accepted (see Part 4), the withdrawal period authorised for EQUIOXX paste (26 days) can be applied to the EQUIOXX tablet formulation when the tablet is administered at a dose that is comparable to the dose administered in the pivotal residue depletion study and is in line with the dose range achieved when EQUIOXX oral paste is administered in accordance with the approved posology. During the procedure, the weight/dose banding of the tablet formulation was revised so that the highest dosage administered using the tablet formulation (0.127 mg/kg) is comparable to the highest dose administered using the paste formulation (0.126 mg/kg). Consequently, considering bioequivalence is accepted, and that the highest administered dose of the tablet is comparable to that of the paste formulation, it is considered acceptable (for the dose range now proposed) to extrapolate the withdrawal period accepted for the paste formulation (26 days).

Overall conclusions on the safety and residues documentation

In support of this extension, pharmacokinetic studies were conducted to compare the bioavailability of the 57 mg tablet in the horse with the bioavailability of the oral paste to allow bridging of the safety data package of the oral paste to the tablet. For a summary of the 'bridging' pharmacokinetic studies, see Part 4. Given that bioequivalence is accepted, this approach is considered generally acceptable.

Part 4 – Efficacy

The purpose of the current application is to obtain an extension of the marketing authorisation of EQUIOXX to a new pharmaceutical form, a 57 mg oral tablet, at the same dose regimen as the oral paste (0.1 mg/kg) and for the same indication ("for the alleviation of pain and inflammation associated with osteoarthritis and reduction of associated lameness in the horse"). EQUIOXX 57 mg tablets for horses are the same formulation as the approved product Previcox tablets for dogs (57 mg). In support of this extension pharmacokinetic studies were conducted to compare bioavailability of the 57 mg tablet in the horse with bioavailability of the oral paste to allow bridging of the efficacy data package of the oral paste to the tablet.

During the assessment procedure, the applicant chose to restrict use of this product to animals in the weight range 450 – 600 kg bodyweight to ensure accurate (safe and effective) dosing.

Pharmacodynamics

No data presented.

Pharmacokinetics

The first of the comparative pharmacokinetic studies was a non-GLP, exploratory study conducted to investigate the comparative bioavailability of the 57 mg firocoxib tablet and the firocoxib oral paste. This study was designed as a two period crossover study and used 12 horses (of which 11 were used in the final analysis). For most animals, the firocoxib concentrations during the first 30 minutes following paste ingestion were higher than those following administration of the tablets. C_{max} with the tablet (59.1 ± 15.9 ng/mL) was about 27% lower than with the paste (80.7 ± 25.6) and T_{max} with the tablet (5.16 +/- 3.10) was about 1.75 hours later than with the paste. It is suggested that the difference in absorption phase (absorption of firocoxib is slower following tablet administration compared to that following administration of the paste) is most likely due to slower dissolution of the tablet prior to being absorbed. Following the absorption phase, the plasma concentration-time curves were comparable. There was no appreciable difference in the terminal plasma half-life, T_{last} or C_{last}.

Regarding the bioequivalence statistics, the point estimates for the geometric mean ratio (test/reference) were 73.6% for C_{max} and 91.9% for AUC_{last}. The 90% confidence intervals of the geometric mean ratio were 63.1 – 85.8% for C_{max}, and 75.3 – 112% for AUC_{last}. Given the difference in absorption phase between products, the lower 90% confidence limits were not within the pre-defined acceptance criteria for AUC and C_{max} of 80 to 125%. Consequently, it was concluded that under the conditions of this study the tablet formulation is not bioequivalent to the oral paste. While the findings of this study do indicate a difference between formulations for the absorption phase, this exploratory study provides useful information/data to inform the experimental design of the pivotal study.

The second comparative pharmacokinetic study is considered the pivotal study. It was conducted in accordance with GLP to demonstrate bioequivalence between an oral firocoxib tablet (1 tablet containing 57 mg firocoxib per horse) and an oral firocoxib paste (1 syringe containing 56.8 mg firocoxib per horse). The design used was a two period crossover with a 28-day wash out between periods. The study was appropriately designed for the purpose of investigating bioequivalence and there were no deviations that would adversely impact on the outcome/interpretation of the study. Firocoxib concentrations in plasma were analysed using a suitably validated LC-MS/MS method. The number of animals included in the study (n=30) is justified in the study protocol and appears appropriate given that bioequivalence in terms of AUC is claimed.

In this study, rather than dose on a mg/kg basis, the same total dose (either 57 mg tablet or 56.8 mg paste) was administered to each animal (independent of body weight) in both study periods. When the total dose administered is compared to the body weight of the test animals (402-596 kg), individual doses administered were in the range 0.1 to 0.15 mg/kg.

For evaluation of bioequivalence, the applicant argues that the standard acceptance criteria of 80-125% are not appropriate given the observed differences in the absorption phase in the exploratory pharmacokinetic study; therefore, the applicant set about establishing surrogate limits to demonstrate acceptable efficacy and safety of the tablet when compared to the paste. The acceptance criteria selected for the pivotal study were 69%-167%, the lower bound of which is considered by the applicant to represent the lowest treatment mean for the tablet and paste that could be considered effective and the upper bound of which is considered to represent highest safe treatment mean for the tablet and paste. While the rational for the applicants approach can be followed, it must be acknowledged that current guidance does not foresee such an approach. VICH GL 52 states that "to be internationally acceptable, the acceptance criteria for AUC and C_{max} should be 0.80 to 1.25". In the current CVMP bioequivalence guideline (EMA/CVMP/016/00-Rev.2), the requirements for accepting bioequivalence are defined as follows:

> "For AUC, the ratio of the two treatment means should be entirely contained within the limits 80% to 125%. The acceptance limits for C_{max} and C_{min} should also generally be within 80% to 125%. However, as these parameters may exhibit a greater intra-individual variability, a maximal widening of the limits to 70% to 143% could in rare cases be acceptable if it has been prospectively defined in the protocol together with a justification from efficacy and safety perspectives."

Therefore, following existing CVMP guidance, the surrogate CIs proposed by the applicant are not accepted and the findings of the pivotal bioequivalence study will be viewed against the limits defined in the CVMP guideline. While AUC will be viewed against the standard limits of 80% to 125%, the rapporteur is prepared to apply the wider limits of 70% to 143% to C_{max} noting that:

1) The absorption phase is expected to be different for the tablet compared to the paste due to slower dissolution resulting in a later T_{max} and a lower C_{max} (for the tablet compared to the paste), and

2) The product is intended to be administered at a treatment interval of 24 hours and the peak concentration achieved (within the first 3 hours after product administration) will not be the main determining factor for overall efficacy of the product. Based on the exploratory pharmacokinetic study, it is noted that following the absorption phase, the plasma concentration-time curves were very similar with no difference between formulations for T½, C_{last} or T_{last}.

As in the previous study, the findings of the pivotal study indicate that C_{max} was lower and T_{max} longer for the tablet compared to the paste and this is attributed to the difference in formulation, the paste dissolving more quickly than the tablet. For the paste formulation the average time to maximum concentration (T_{max}) was 1.09 hours (range 0.25-2 h, one animal at 4 h) and the maximum concentration (C_{max}) was 96.1 ng/ml. For the tablet product the average T_{max} was 2.43 hours (range 0.25-4 h, one animal at 6 h, one animal at 12 h) and the C_{max} was 75.3 ng/ml. The area under the curve from time 0 to the last quantifiable time point (AUC_{last}) was 3110 and 3010 ng*h/ml for the paste and tablet formulations, respectively. The mean concentration-time profiles were parallel and nearly superimposable after the time to maximum concentration (T_{max}). The mean pharmacokinetic parameters indicate the same extent of exposure (area under the curve) and half-life for the two formulations.

Relative bioavailability was established for the tablet formulation based on dose normalised AUC_{last} and dose normalised C_{max}. The average AUC_{last} ratio of test (tablet) to reference (paste) product was 97.9% and the lower and upper 90% confidence intervals were 91 .7 and 105%, respectively, and completely contained within the predefined limits of 69-167%. The average C_{max} ratio of test (tablet) to reference (paste) product was 78.6% and the upper 90% confidence interval (86.8%) was below the pre-assigned limit of 167%. The uncorrected AUC_{last} geometric mean ratio (tablet/paste) was 96.6% (90% confidence intervals; 89.6, 104). The uncorrected C_{max} geometric mean ratio (tablet/paste) was 77.5% (90% confidence intervals; 70.0, 85.8). The ratios between the dose normalized and uncorrected parameters differ by less than 2%. The relevant CVMP guideline recommends the use of uncorrected (not dose normalised) data.

In this pivotal study, the mean pharmacokinetic parameters suggest the same extent of exposure (area under the curve) and half-life for the two formulations. Indeed, while the applicant has argued that wider confidence intervals could be applied to the interpretation of bioequivalence in the current study, it is evident that the upper and lower limits for the AUC ratio, 89.6% and 104%, respectively, fall within the traditional acceptance limits (80-125%) recommended by the CVMP (VICH GL52) to demonstrate bioequivalence.

In conclusion, using uncorrected (not dose normalised) data, the 90% confidence intervals for the AUC_{last} geometric mean ratio was within the standard acceptance limits of 80-125%, whereas for C_{max}, the 90% confidence intervals for the geometric mean ratio was within the wider limits of 70-143%. Therefore, it is accepted that the tablet formulation is bioequivalent to the paste formulation when both products are administered in the dose range 0.1-0.15 mg/kg. Given that bioequivalence is accepted, the safety and efficacy data package of the paste formulation can be extrapolated to the tablet formulation and a similar safety and efficacy profile is to be expected when the products are administered at the target dose of 0.1 mg/kg. On this point, it is noted that the reference product allows for accurate dosing at weight intervals of 100 kg (as reflected in Section 4.9 of the reference SPC: "each full dose division on the syringe plunger delivers sufficient firocoxib to treat 100 kg"). As acknowledged by the applicant, the majority of the target population will be within the 300-600 kg dose band. When administering the paste formulation to horses in this weight range, the mg/kg dose ranges from approximately 0.095 to 0.126 mg/kg.

In order to ensure that the proposed dose range for the tablet formulation is in line with the accepted dose range for the paste formulation (that is, at or within the limits 0.095 – 0.126 mg/kg), the applicant has chosen to restrict use of the product, which will be available for use in horses as a single strength tablet (57 mg), to animals in the weight range 450 – 600 kg bodyweight (resulting in a dose range of 0.095 – 0.127 mg/kg). This weight range is likely to include most of the target population (sport horses). However, given that additional strengths of the tablet formulation are not available (or, at least, envisaged for use in the horse), it is not possible to cover 100% of the horse population. It is accepted that this should not be a concern given that other firocoxib formulations are available (oral paste and solution for injection) which effectively cover the entire horse population and can be used for animals outside of the proposed weight band for the 57 mg tablet. Accordingly, information is included in the SPC advising on treatment options for horses weighing less than 450 kg or more than 600 kg.

The CVMP is prepared to accept this approach noting that:

- The target population will be clearly indicated in the product literature,
- The product literature will include a clear statement to the effect that the product should not be used in animals outside of the intended dose range, and

- The concept of weight (and/or age) restrictions on the use of specific products or product presentations is widely applied/accepted (for example, "do not use in animals less than x kgs/days/months").

In conclusion, the CVMP agrees that the tablet formulation is bioequivalent to the paste formulation when both products are administered in the same dose range. The proposal to restrict use of this product to animals in the weight range 450-600 kg (resulting in a dose range of 0.095 – 0.127 mg/kg) can be accepted.

Target animal tolerance

In terms of target animal safety, the substance of concern in the formulation is firocoxib and the excipients in the tablet are considered safe due to their regulatory acceptance and common use in pharmaceuticals and food.

The applicant argues that as relative bioavailability between the tablet and the oral paste has been demonstrated in the pivotal bioequivalence study based on acceptable 90% confidence intervals, the tolerance data generated with the oral paste can be applied to the 57 mg tablet (that is, a comparable safety profile in the target species is anticipated). For the oral paste a comprehensive target animal safety data package was provided. In the EPAR for EQUIOXX oral paste, these data are summarised as follows:

> "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."

Given the findings of the comparative pharmacokinetic studies, and noting that the excipients are safe in the quantities included in the tablet formulation, it is accepted that the safety profile of both products will be comparable when administered at the same mg/kg dose.

Given that the upper limit of the 'established' dose range of the paste formulation (0.126 mg/kg) is comparable to that currently proposed for the tablet formulation, the proposed dose range can be accepted as safe.

It is also noted that when tablets are administered to horses, it is possible that some of the tablets may become trapped in areas in the buccal cavity (e.g. under the tongue or in the sublingual areas). It is noted that treatment related oral lesions may occur following use of the recommended dosage of EQUIOXX oral paste, while systemic toxicity has been seen at 2.5 and 3 times the recommended treatment dose of 0.1 mg/kg.

When addressing the concern relating to local tolerance, the applicant argued that oral lesions associated with firocoxib administration are not the result of a direct local effect on the mucosa (such lesions are also seen with EQUIOXX solution for injection) and that the only concern associated with tablet retention in the mouth would be lack of efficacy. To address this concern, Section 4.9 of the SPC includes the following statement: "After administration, it is recommended to examine the buccal cavity to ensure that the tablet has been adequately swallowed". This is accepted.

Clinical field trials

No data provided.

The applicant argues that as relative bioavailability between the tablet and the oral paste has been demonstrated in the pivotal bioequivalence study based on acceptable 90% confidence intervals, the efficacy data (dose confirmation and field trials) generated with the oral paste can be applied to the 57 mg tablet. These studies have already been submitted to and assessed by the CVMP. In the context of this extension application, they are not submitted again. This approach is considered acceptable.

Overall conclusion on efficacy

Based on the findings of the pivotal comparative pharmacokinetic study, it is accepted that the tablet formulation is bioequivalent to the paste formulation when both products are administered in the dose range 0.1-0.15 mg/kg. Given that bioequivalence is accepted, the safety and efficacy data package of the paste formulation can be extrapolated to the tablet formulation and a similar safety and efficacy profile is to be expected when the products are administered at the target dose of 0.1 mg/kg. On this point, it is noted that the reference product allows for accurate dosing at weight intervals of 100 kg (as reflected in Section 4.9 of the reference SPC: "each full dose division on the syringe plunger delivers sufficient firocoxib to treat 100 kg"). It is acknowledged that the majority of the target population will be within the 300-600 kg dose band. When administering the paste formulation to horses in this weight range, the mg/kg dose ranges from approximately 0.095 to 0.126 mg/kg.

The proposed weight banding for the tablet formulation has been revised by the applicant in light of safety (consumer and target animal) concerns raised in the original LOQ. In order to ensure that the proposed dose range for the tablet formulation is in line with the accepted dose range for the paste formulation (that is, at or within the limits 0.095 – 0.126 mg/kg), the applicant has chosen to restrict use of the product, which will be available for use in horses as a single strength tablet (57 mg), to animals in the weight range 450 – 600 kg bodyweight (resulting in a dose range of 0.095 – 0.127 mg/kg). This weight range is likely to include most of the target population (sport horses). However, given that additional strengths of the tablet formulation are not available (or, at least, envisaged for use in the horse), it is not possible to cover 100% of the horse population. It is accepted that this should not be a concern given that other firocoxib formulations are available (oral paste and solution for injection) which effectively cover the

entire horse population and can be used for animals outside of the proposed weight band for the 57 mg tablet. Accordingly, information is included in the SPC advising on treatment options for horses weighing less than 450 kg or more than 600 kg.

The CVMP is prepared to accept this approach.

In conclusion, it is expected that the new formulation (chewable tablet) will have the same safety profile and provide the same efficacy as the approved formulation (oral paste), when administered to the target population according to the proposed conditions of use.

Part 5 – Benefit-risk assessment

Introduction

Firocoxib is a non-steroid anti-inflammatory substance (NSAID) marketed for horses under the trade name EQUIOXX (currently authorised as an oral paste and an injectable solution). The purpose of the current application is to obtain an extension of the marketing authorisation of EQUIOXX to a new pharmaceutical form, a 57 mg oral tablet, at the same dose regimen as the oral paste (0.1mg/kg) and for the same indication ("for the alleviation of pain and inflammation associated with osteoarthritis and reduction of associated lameness in the horse").

The application for an extension to the marketing authorisation for EQUIOXX has been submitted in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I point 2(d) change or addition of a new pharmaceutical form thereof.

Benefit assessment

Direct therapeutic benefit

The proposed benefit of EQUIOXX tablets for horses is its efficacy for the alleviation of pain and inflammation associated with osteoarthritis and reduction of associated lameness in the horse. In support of this extension, pharmacokinetics studies were provided comparing bioavailability of the 57 mg tablet with bioavailability of the oral paste in the horse to allow bridging of the safety and efficacy data package of the oral paste to the tablet.

The evidence for the direct therapeutic benefit is considered established on the basis of bioequivalence to the reference product when administered at the same dose and by the same route of administration as already approved for the oral paste.

Additional benefits

The new pharmaceutical form of EQUIOXX as 57 mg tablets increases the range of available treatment possibilities and dosing options for the alleviation of pain and inflammation associated with osteoarthritis and reduction of associated lameness in the horse.

Risk assessment

Quality:

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and

uniformity of important product quality characteristics, and these in turn lead to the conclusion that the new tablet formulation should have a satisfactory and uniform performance in clinical use.

Safety:

Risks for the target animal:

The recommended maximum dose of firocoxib for the target population (horses in the weight range 450-600 kg) does not exceed the recommended maximum treatment dose for EQUIOXX oral paste (assuming that the product is administered as per label). Consequently, the risks to the target animal associated with the use of the new tablet formulation can be considered comparable to the risks associated with the use of the authorised paste formulation.

Risk for the user:

The CVMP concluded that user safety for the new tablet formulation is acceptable when used according to the SPC recommendations. Standard safety advice is included in the SPC.

However, it is recommended to re-start the periodic safety update report (PSUR) cycle for EQUIOXX to ensure more frequent pharmacovigilance monitoring due to the narrow safety margin of firocoxib and new pharmaceutical form. The data lock point (DLP) for the first 6-monthly PSUR of the re-started cycle would be 31/12/2017.

Risk for the environment:

EQUIOXX 57 mg tablets for horses are not expected to pose a risk for the environment when used according to the SPC.

Risk for the consumer:

The withdrawal period established to ensure depletion of residues below the MRLs is 26 days.

Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of the new tablet formulation relevant to the target animal, user environment and consumer when the product is administered at a target dose of 0.1 mg firocoxib/kg and to provide advice on how to prevent or reduce associated risks.

Evaluation of the benefit-risk balance

The efficacy of the new tablet formulation has been justified in the following indication: "Alleviation of pain and inflammation associated with osteoarthritis and reduction of associated lameness in the horse (weighting from 450 to 600 kg)".

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The product is well tolerated by the target animals and presents an acceptable risk for users, consumers and the environment when used as recommended.

Appropriate warnings and precautionary measures have been included in the SPC and other product information.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for EQUIOXX is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.

Divergent position on a CVMP opinion on the extension to the community marketing authorisation for EQUIOXX (EMEA/V/C/000142/X/0015)

The undersigned wish to express a divergent position to the CVMP Opinion on this application for a marketing authorisation for EQUIOXX chewable tablets for horses.

In the opinion of the undersigned, the approval of these Firocoxib chewable tablets for horses is not justified on the grounds of bioequivalence. Also, hickory smoke flavouring is an unusual choice for a horse product, since it is a completely unnatural flavour for the horse. There is neither any palatability study in this dossier, nor justification for the use of hickory-smoke flavour for this product.

Two bioequivalence studies were performed. It is unclear as to assurances that the horses ingested the entire dose. For example, it is well known that not all (100%) of feed material in the horse's mouth is ingested, where chewable materials are commonly lodged between teeth and in the buccal cavity. Also, "quidding" (dropping food out of the mouth) is very common in horses. In the first bioequivalence study, the 90% confidence intervals of the geometric mean ratio of C_{max}, and AUC_{last} were lower than 90% confidence limits and not within the pre-defined acceptance criteria for AUC and C_{max} of 80 to 125%. Consequently, it was concluded that under the conditions of the study that the chewable tablet formulation was not bioequivalent to the comparator oral paste. The second comparative pharmacokinetic study was considered the pivotal study. In the second study, there was allowance for wider limits of 70 to 143% to C_{max} noting that:

1) The absorption phase is expected to be different for the tablet compared to the paste due to slower dissolution resulting in a later T_{max} and a lower C_{max} (for the tablet compared to the paste), and

2) The product is intended to be administered at a treatment interval of 24 hours and the peak concentration achieved (within the first 3 hours after product administration) will not be the main determining factor for overall efficacy of the product. Based on the exploratory pharmacokinetic study, it is noted that following the absorption phase, the plasma concentration-time curves were very similar with no difference between formulations for T½, C_{last} or T_{last}.

In the second study, the uncorrected AUC_{last} geometric mean ratio (tablet/paste) was 96.6% (90% confidence intervals; 89.6, 104). The uncorrected C_{max} geometric mean ratio (tablet/paste) was 77.5% (90% confidence intervals; 70.0, 85.8). Four horses were not given 100% of the reference product dose.

Nevertheless, the undersigned do not agree to the reasons for widening the limits of C_{max}. The formulation does make an important impact on the bioavailability of the chewable tablets. For example, in both bioequivalence studies the C_{max} was lower and T_{max} longer for the tablet compared to the paste and considered to be attributed to the differences in formulation, with the paste dissolving more quickly than the tablet. C_{max} in both studies fell outside of the accepted VICH GL 52 guideline of 80-125%.

London, 8 December 2016

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