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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Coxatab (EMEA/V/C/005816/0000)

INN: firocoxib

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Introduction

The applicant CP-Pharma Handelsgesellschaft mbH submitted on 17 June 2021 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Coxatab through the centralised procedure under Article 3(3) of Regulation (EC) No 726/2004.

The eligibility to the centralised procedure was agreed upon by the CVMP on 11 December 2020 as the product would constitute a generic/hybrid product of a product authorised through the centralised procedure Previcox (reference product).

The applicant applied for the following indications:

- For the relief of pain and inflammation associated with osteoarthritis in dogs.
- For the relief of post-operative pain and inflammation associated with soft-tissue, orthopaedic and dental surgery in dogs.

The active substance of Coxatab is firocoxib, a non-steroidal anti-inflammatory drug (NSAID) belonging to the coxib group, which acts by selective inhibition of cyclooxygenase-2 (COX-2) – mediated prostaglandin synthesis. The target species is dogs.

Coxatab chewable tablets contain 25 mg, 57 mg, 100 mg or 225 mg of firocoxib. For each strength there are pack sizes containing 10, 20, 30, 50, 100 and 200 chewable tablets which are packed in blister strips of 10 tablets each. The blisters are packed in cardboard boxes.

The rapporteur appointed is Leona Nepejchalová and the co-rapporteur is João Pedro Duarte Da Silva.

The dossier has been submitted in line with the requirements for submissions under Article 13(1) of Directive 2001/82/EC – a generic application (57 mg strength) and Article 13(3) of Directive 2001/82/EC – a hybrid application (25 mg, 100 mg and 225 mg strengths).

On 15 June 2022, the CVMP adopted an opinion and CVMP assessment report.

On 12 August 2022, the European Commission adopted a Commission Decision granting the marketing authorisation for Coxatab.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (dated 2 January 2021) which fulfils the requirements of Directive 2001/82/EC. Based on the information provided 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.

Manufacturing authorisations and inspection status

Manufacture of the dosage form, primary and secondary packaging, and quality control take place in the EEA. The site is authorised for the activities indicated.

Batch release takes place at CP-Pharma Handelsgesellschaft mbH, Burgdorf (Germany). The site holds a manufacturing authorisation issued on 16 November 2020 by the competent authority in Germany. GMP certification, 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.

GMP compliance declaration for the active substance manufacturing and micronisation sites was provided from the Qualified Person (QP) at the EU batch release site.

Overall conclusions on administrative particulars

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

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

Part 2 - Quality

Composition

The finished product is presented as off-white to light brown, speckled with brown spots, round and convex chewable tablets with a cross-shaped break line on one side containing either 25, 57, 100 or 225 mg of firocoxib as active substance.

Other ingredients are lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose, colloidal hydrated silica, magnesium stearate (non-animal origin) and chicken flavour.

The product is available in aluminium - PVC/PE/PVDC blisters put in cardboard box.

Containers

The primary packaging is a blister constructed of top film made from PVC, PE and PVDC and a bottom made from aluminium foil. The material of the blisters complies with the EU legislation applicable to materials intended to come into contact with food.

The blisters each with 10 tablets are put in a cardboard box. The cardboard box contains either 1, 2, 3, 5, 10 or 20 blisters.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Development pharmaceutics

The product is formulated with a view to mirroring the formula of the reference product, Previcox 57 mg tablets, as authorised in the EU. The same active substance in the same concentration (and same polymorphic form) is used and most of the excipients are also the same qualitatively with the exception in colouring and flavouring system. All excipients are well known pharmaceutical ingredients

and their quality is compliant with Ph. Eur. standards (except for chicken flavour, which is compliant with an in-house standard). There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC.

Based on the results of testing of the originator product, the applicant conducted several trials to formulate sufficiently similar tablets. A similarly behaving product was obtained, which was further supported by comparison testing of several parameters.

The conditions for the dissolution testing are sufficiently justified.

As the applicant concluded that a biowaiver between originator and generic product is not justified, one strength (57 mg) was subjected to an *in-vivo* bioequivalence study, while the remaining strengths were compared to the biobatch in regard to the similarity of their dissolution profiles.

Similarity between strengths was evaluated using the f2 approach as described in the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.3-corr.*). The results show that the remaining strengths are sufficiently similar to the biobatch at all pH values.

Divisibility of the tablets was tested and confirmed in accordance with Ph. Eur. test on subdivision of tablets.

The active substance particle size was checked on five batches and it was confirmed that it is produced in reproducible particle size. Similarly, microbiological quality was checked on four batches of active substance to confirm that as a dry substance it is not susceptible to microbiological growth.

As it is demonstrated that the related substances do not increase during manufacturing process, their non-routine control at release is acceptable.

It is accepted not to test the moisture content at release and during shelf life as the product is made using dry granulation from dry ingredients and no significant increase of moisture content is observed during stability testing.

A summary of the risk assessment on control of elemental impurities is provided and is considered acceptable.

A summary of residual solvents likely to be present in the finished product is provided.

Method of manufacture

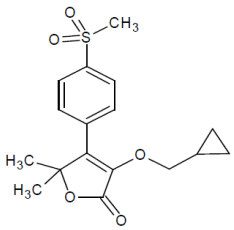
The manufacturing process consists of blending the ingredients, dry granulation, mixing the final tableting blend and compression into tablets, storage of tablets in bulk, and later packaging into blisters. The process is considered to be a standard manufacturing process; however, process validation was conducted on two production size batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. A maximum holding time for the bulk tablets has been proposed and accepted.

Control of starting materials

Active substance

The active substance firocoxib is not described in the Ph. Eur. or in the National Pharmacopoeia of any EU member state. The chemical name of the substance is 3-cyclopropylmethoxy-5,5-dimethyl-4[4-(methyl sulfonyl)phenyl]-2-(5H)-furanone. It is white to off-white crystalline powder and has the following chemical structure:



Firocoxib exists in two polymorphic forms, form A and form B. During manufacture of the active substance, the same polymorphic form is produced. The molecule does not exhibit any chiral centre. Firocoxib is practically insoluble in water, soluble in ethyl acetate, freely soluble in chloroform and dimethyl sulfoxide (DMSO).

One source of firocoxib is proposed. The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

ASMF

The manufacturing process of firocoxib consists of 7 steps of synthesis followed by purification. The starting materials are defined in line with principles given in ICH Q11. The detailed process description, control of materials, process controls and intermediates are given in sufficient detail in the restricted part.

It is further confirmed that the same polymorphic form is produced by the given manufacturing process and it does not change during the micronisation (when applied).

Potential organic impurities are listed with an explanation of their origin and control strategy. Satisfactory discussion is given for the carry-over of residual solvents across the route of synthesis. The ASMF holder has provided a satisfactory summary of the risk assessment supported by analytical data on the presence of elemental impurities.

The active substance specification covers the relevant quality parameters with acceptable criteria. The following tests are included: appearance, identification, heavy metals, sulfated ash, melting point, loss on drying, particle size, residual solvents, assay and related substances.

Impurities are controlled as per thresholds established in ICH Q3A that is stricter than the VICH GL10. The limit for assay and the respective analytical method are usual for this kind of substance.

The control methods are sufficiently described. Validations are provided for HPLC on assay and impurities, GC on residual solvents and laser diffraction on particle size. The validations follow principles in VICH GL1 and GL2 and they are satisfactory.

Batch analysis results are given for three batches of micronised and three batches of non-micronised firocoxib. The results are compliant with the specification.

Satisfactory data are provided for reference substance firocoxib.

Firocoxib is packaged into fibre drums lined with double layer of polyethylene bag. The PE material is declared compliant with the EU Regulation 10/2011 on plastic materials and articles intended to come into contact with food. Satisfactory specifications for the packaging materials and components are provided.

Stability studies are carried out as per VICH GL3. The primary three batches (before scale-up) are placed under accelerated (40 °C/75% RH) and long-term (25 °C/60% RH) conditions. The studies under accelerated conditions are completed (12 months) and the long-term studies are planned up to 60 months with data available up to 36 months. Three additional batches are placed for annual long-term studies with data available up to 24 months (two batches) and 12 months (one batch). No significant changes are observed for any batch under long-term or accelerated conditions. The retest period of 4 years with no temperature storage restrictions is acceptable following the extrapolation of real time data as per VICH GL51.

As regards the stress studies, it is observed that the substance is sensitive to exposure to acidic and alkaline conditions (assay decreases, impurities are formed). Under increased temperature, the appearance is changed but with no impact on purity. Firocoxib is not sensitive to light, oxidation and increased humidity. The HPLC control method is confirmed to be stability indicating.

The applicant's own specification of the active substance is the same as the one in the ASMF with no additional testing.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. monographs where applicable with some additional functional characteristics. The chicken flavour is the only excipient used that is not monographed in Ph. Eur. The specification of the chicken flavour excipient covers relevant parameters and is sufficiently justified. Manufacturing flowchart of the excipient is also provided as well as statement that the chicken protein used is from EU origin and was taken from animals fit for human consumption. A viral safety evaluation for chicken flavour is also provided.

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

The only material of animal origin used in the product is lactose monohydrate and chicken flavour. It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.

Control tests on the finished product

The specification proposed for use at release covers relevant parameters of the dosage form. Suitable limits are established as per the findings in the product development, requirements in the Ph. Eur. texts and CVMP/VICH guidelines.

The finished product release specification includes tests for appearance, tightness of blister, average mass, resistance to crushing, uniformity of dosage units, identification of firocoxib, assay, impurities, dissolution and microbiological purity.

The analytical methods used have been described and validated in accordance with the VICH

guidelines.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided from two commercial batches of the powder blend compressed into all four strengths confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

The specification proposed at the end of shelf-life is the same as that proposed at release except omission of average mass and resistance to crushing. The limits are the same as for release except relaxation of total impurities. Additional parameters are checked for stability purposes only: subdivision of tablets (Ph. Eur.) and Loss on drying (Ph. Eur., for information only). The differences between release and end of shelf-life specifications have been appropriately justified.

Stability data were provided for two commercial scale batches of the powder blend both compressed into the 25 mg and 225 mg strengths. From each batch of powder blend 2 batches of tablets were produced one of the 25 mg strength and another one of the 225 mg strength. These tablet batches were stored under long term conditions for 24 months at 25 ºC/60% RH and for up to 6 months under accelerated conditions at 40 ºC/75% RH according to the VICH GL3 on stability testing of new veterinary drug substances and medicinal products. The batches of product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for the same parameters and limits as described in the specification for batch release except the average mass and uniformity of dosage units. No significant changes have been observed during the stability studies, only slight variability of the results, which can be attributed within the confidence limits of the methods. The content of impurities remains in both studies below disregard limits of 0.1%.

In addition, the same batches were exposed to light as defined in the VICH GL5 on photostability testing of new veterinary drug substances and medicinal products. The results under all conditions remained similar and thus showed that the product is not sensitive to light – no light storage restrictions need to be applied.

In-use stability was also tested on these batches and it showed that the product is stable when outside of the packaging for three days.

Based on the available stability data, the proposed shelf-life of 3 years is acceptable.

It is concluded that no special storage conditions are necessary for the product.

Overall conclusions on quality

The application for Coxatab has been submitted as a generic/hybrid application under Article 13 of Directive 2001/82/EC.

The finished product is presented as chewable tablets containing 25 mg, 57 mg, 100 mg or 225 mg of firocoxib as active substance. The excipients are lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose, colloidal hydrated silica, magnesium stearate (non-animal origin) and chicken flavour. The tablets are packed in aluminium - PVC/PE/PVDC blisters and put in cardboard box.

The product is formulated with a view to mirroring the formula of the reference product, Previcox 57 mg tablets. The same active substance in the same concentration (and same polymorphic form) is used and most of the excipients are also the same qualitatively with the exception in colouring and flavouring system.

Based on the results of testing of the originator product and comparison testing with the test product a similarly behaving product was obtained.

The conditions for the dissolution testing are sufficiently justified.

One strength (57 mg) was subjected to an *in vivo* bioequivalence study, while the remaining strengths were compared to the biobatch in regard to the similarity of their dissolution profiles using the f2 approach. The results show that the remaining strengths are sufficiently similar to the biobatch at all pH values.

The manufacturing process consists of blending the ingredients, dry granulation, mixing the final tableting blend and compression into tablets, storage of tablets in bulk, and later packaging into blisters. Process validation was conducted on two production size batches. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Information on the control of starting materials has been provided.

Data on the active substance is provided according to the Active Substance Master File (ASMF) procedure. Acceptable information on characterisation, development, manufacture, control and stability of the active substance has been provided. Satisfactory batch analysis data for three batches of micronised and three batches of non-micronised firocoxib have been provided. The dosage form manufacturer own specification of the active substance is the same as the one in the ASMF with no additional testing. A retest period of 4 years with no temperature storage restrictions is acceptable.

All excipients are well known pharmaceutical ingredients and their quality is acceptable.

Sufficient information has been presented to give reassurance on TSE safety.

Batch analysis results are provided from two commercial batches of the powder blend compressed into all four strengths confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Based on the stability data available, the proposed shelf-life of 3 years with no special storage conditions is acceptable.

Information on the development, manufacture and control of the active substance and the 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 product should have a satisfactory and uniform performance in clinical use.

Part 3 – Safety

Safety documentation

This application has been submitted in accordance with Article 13 of Directive 2001/82/EC as a generic/hybrid application. The reference product is Previcox 57 mg chewable tablets for dogs. Coxatab chewable tablets containing 25, 100 and 225 mg of active substance (firocoxib) are dose proportional strengths of the Coxatab 57 mg tablet strength. According to the legal basis of the application, generic/hybrid, the results of safety tests are not required given that the highest strength of the

candidate product is no greater than that of the reference product (Previcox 227 mg), the difference in excipients between the formulations does not represent a safety concern and the products are shown to be bioequivalent.

No new pharmacological or toxicological data are provided in the dossier and the applicant refers to data from the reference product. The MRL summary report for firocoxib is provided and summarised as supportive information (EMA/CVMP/383063/2006-Final). A user risk assessment (URA) has been included in Part 3.A.5 of the dossier.

Pharmacodynamics

See part 4.

Pharmacokinetics

See part 4.

Toxicological studies

No data was presented. The active substance firocoxib was previously assessed by the CVMP in the context of the establishment of MRLs (see European Public MRL Assessment Report (EPMAR) (EMA/CVMP/383063/2006-Final)). Toxicological reference values established in the EPMAR are used are in the user safety assessment.

Excipients

The excipients lactose monohydrate, cellulose, microcrystalline, hydroxypropyl cellulose, croscarmellose sodium, silica, colloidal hydrated and magnesium stearate are widely used in oral pharmaceutical products intended for use in humans and are not considered to represent a safety concern. Natural chicken flavour is also considered safe.

User safety

The applicant has submitted a user risk assessment (URA) which has been conducted in accordance with the current CVMP guideline on user safety (EMEA/CVMP/543/03-Rev.1). The applicant has proposed the same user safety warnings in the product information as those included for the reference product which is considered acceptable.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food animals (i.e. dogs). The product, Coxatab chewable tablets for dogs, is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

This application has been submitted in accordance with Article 13 of Directive 2001/82/EC, generic/hybrid application. The applicant has not submitted a complete safety file which is considered acceptable because bioequivalence between the formulations is demonstrated (see Part 4), the highest strength of the candidate product is no greater than that of the reference product and the difference in excipients between the formulations does not represent a safety concern. A user risk assessment (URA) has been included in Part 3.A.5 of the dossier.

An appropriate environmental risk assessment was provided. The product is not expected to pose a risk for the environment when used according to the SPC.

The safety of the product is comparable to that of the reference product and the same user safety warnings are therefore appropriate.

Part 4 – Efficacy

This application has been submitted as a hybrid/generic application. The reference product is Previcox 57 mg chewable tablets for dogs. Given that bioequivalence between candidate and reference formulations has been demonstrated, the extrapolation of data from the dossier of the reference product to the candidate product is appropriate.

Pharmacodynamics

No proprietary studies have been submitted. As this is a hybrid/generic application and bioequivalence between the candidate product and the reference product has been demonstrated, it can be accepted that the pharmacodynamic properties of the active substance firocoxib have already been adequately characterised and that cross-reference to the dossier of the reference product and omission of specific data on the pharmacodynamic properties of the candidate product are appropriate. The information proposed for inclusion in section 5.1 of the SPC is identical to that approved for the reference product.

Pharmacokinetics

In support of this application, the applicant conducted two *in vivo* bioavailability studies in order to compare the plasma concentration profile of firocoxib between the candidate formulation firocoxib 57 mg and the reference product Previcox 57 mg.

Bioequivalence studies

The applicant has provided the results of 2 bioequivalence studies compliant with Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.3-corr.*):

- an *in vivo* bioequivalence study conducted using the 57 mg tablet strength candidate and the 57 mg tablet strength reference formulation; Study A.
- a pivotal *in vivo* bioequivalence study conducted using the 57 mg tablet strength candidate and the 57 mg tablet strength reference formulation; Study B.

In order to bridge data from the reference product Previcox 57 mg to the additional strengths of Coxatab (25, 100 and 225 mg), the applicant has performed a solubility study, which is summarised in part 2.

A single dose, two period, two sequence, crossover bioequivalence study of two firocoxib containing tablets after oral administration in beagle dogs (Study A):

This was a GLP compliant study using 24 beagle dogs. The study was designed as a cross-over study with two treatment periods (1 and 2) and a wash out period of 7 days between treatment periods. Animals were already acclimatised as they originate from the animals housed in test facility. Animals were randomly assigned (12 animals in each group) using a blocking system based on gender and weight.

Following weighing, all animals were administered the test/reference articles at the following scheme: animals with a bodyweight ≤10 kg received 1 tablet and animals with a bodyweight >10 kg received 1½ tablet which corresponds a dose rate of 5.7 – 8.76 mg firocoxib/kg bodyweight in line with the SPC of the reference product.

Blood samples for plasma firocoxib determination were collected from the jugular vein on 14 occasions in each period of the study; once pre-treatment and then at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 5, 7, 12, 16, 24 and 36 hours after article administration. The firocoxib content in the blood samples was determined using a LC-MS/MS method validated in the concentration range 2 – 2000 ng/ml.

The plasma concentrations of firocoxib were used to calculate the pharmacokinetic parameters C_{max}, T_{max}, AUC_{last}. In several animals (approximately half, for both the test item and the reference item), plasma concentration profiles for firocoxib followed a two-peak pattern, most likely explained by enterohepatic recirculation. As a result, the regression could not be reliably calculated and AUC_{∞} and $t_{1/2}$ were not reported.

Demonstration of bioequivalence was specified as having been achieved if the 90% confidence intervals for AUC_{last} are within the ratio of the test mean to control mean of 0.8 to 1.25 and if the 90% confidence intervals for C_{max} are within the ratio of 0.7 to 1.43.

The peak plasma concentration, C_{max}, was reached at 1 to 3 hours after dosing of the reference item and generally at 0.75 to 3 hours (ranging between 0.75 to 24 hours) after dosing of the test item.

The 90% confidence interval on the log-transformed scale of the geometric mean ratio of AUC_{last} was 89.6-132% and therefore slightly exceeded the accepted confidence interval. For C_{max}, the 90% confidence interval on the log-transformed scale of the geometric mean ratio was between 70-143%. Based on the results presented it cannot be concluded that the test and reference items are bioequivalent.

A single dose, two period, two sequence, crossover bioequivalence study of two firocoxib containing tablets after oral administration in beagle dogs (Study B):

This was a GLP compliant study using 36 beagle dogs. The study was designed as a cross-over study with two treatment periods (1 and 2) and a wash out period of 7 days between treatment periods. Animals were already acclimatised as they originate from the animals housed in test facility. Animals were randomly assigned (18 animals in each group) using a blocking system based on gender and weight.

Following weighing, all animals were administered the test/reference articles at following scheme: animals with a bodyweight ≤10 kg received 1 tablet (57 mg) and animals with a bodyweight >10 kg received 1½ (85.5 mg) tablet which corresponds a dose rate of 5.7- 8.46 mg firocoxib/kg bodyweight in line with the SPC of the reference product.

Blood samples for plasma firocoxib determination were collected from the jugular vein on 20 occasions in each period of the study; once pre-treatment and then at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 5, 7, 9, 12, 16, 20, 24, 28, 32, 36 and 48 hours after article administration. The firocoxib content in blood samples was determined using a LC-MS/MS method validated in the concentration range 2 – 2000 ng/ml.

The plasma concentrations of firocoxib were used to calculate the pivotal pharmacokinetic parameters C_{max}, T_{max}, T_{last}, AUC_{last}, $T_{1/2}$ and AUC_{∞}.

Determination of bioequivalence was based on the pivotal parameters C_{max} and AUC_{last}. Demonstration of bioequivalence was specified as having been achieved if the 90% confidence intervals for AUC_{last} are within the ratio of the test mean to control mean of 0.8 to 1.25 and if the 90% confidence intervals for C_{max} are within the ratio of 0.7 to 1.43. The acceptance limits of 70 – 143% for the confidence interval for C_{max} was chosen by the applicant based on the expected variance and previously conducted pharmacokinetic study (Study A).

The peak concentration, C_{max}, was reached at 1 to 5 hours after dosing of the reference item and 0.75 to 5 hours after dosing of the test item, except in one animal where C_{max} was reached at 32 hours after administration of the test item. T_{last} ranged between 36 to 48 hours for the reference item and 32 to 48 hours for the test item. Apparent individual terminal half-lives ranged between 4.4 and 18.3 hours after dosing of the reference item and between 4.0 and 12.2 hours after dosing of the test item.

The results of the comparative bioavailability study indicate that the 90% confidence intervals for the estimate of the ratio of the means for AUC_{last} (103 – 123%) lie within the narrower limits of 80% to 125% and fell within the widened acceptance limits of 70 – 143% for C_{max} (109-139%).

Therefore, based on the results presented it can be accepted that the candidate and the reference product can be considered bioequivalent.

Target animal tolerance

No data on target animal tolerance has been provided.

Given that bioequivalence between candidate and reference formulations has been demonstrated and due to the same proposed route of administration (oral), the omission of target animal tolerance data can be accepted as no difference in tolerance between candidate and reference products is expected.

Overall conclusion on efficacy

In accordance with the legal basis of the application, the applicant has not submitted any pharmacodynamics, target animal safety or clinical field trials. This is considered acceptable.

In support of the efficacy of the product, the applicant conducted two *in vivo* bioequivalence studies to compare the pharmacokinetic profile of the test formulation with the reference product. In the first two-period, two-sequence, single dose, crossover bioequivalence study (Study A), the 90% confidence interval for the ratio of means (test/reference item) slightly exceeded the accepted confidence interval of 80 -125% for AUC_t and fell within the widened acceptance limits of 70 - 143% for C_{max}.

In the second two-period, two-sequence, single dose, crossover bioequivalence study (Study B), the 90% confidence interval for the ratio of means (test/reference item) fell within the accepted confidence interval of 80 -125% for AUC_t and fell within the widened acceptance limits of 70 – 143% for C_{max}. The widening of the acceptance limit for C_{max} is accepted on the grounds that the active substance has shown a high intra-individual variability and the wider acceptance limits were pre-specified in the study

plan.

Consequently, the characteristics of the product with reference to the efficacy and target animal tolerance are considered to be the same for the candidate and reference product.

The SPC includes the same information as that of the reference product Previcox 57 mg. As additional strengths of the product are presented (25, 100 and 225 mg), the corresponding SPC points were amended by the applicant.

Part 5 – Benefit-risk assessment

Introduction

Coxatab chewable tablets contains 25 mg, 57 mg, 100 mg or 225 mg of firocoxib as active substance.

Firocoxib is a non-steroidal anti-inflammatory drug (NSAID) belonging to the coxib group which acts by selective inhibition of cyclooxygenase-2 (COX-2) – mediated prostaglandin synthesis.

The product is intended for use in dogs for the relief of pain and inflammation associated with osteoarthritis and for the relief of post-operative pain and inflammation associated with soft-tissue, orthopaedic and dental surgery. The proposed effective dose is 5 mg/kg bw orally once daily.

The application has been submitted in accordance with Article 13(1) and Article 13(3) of Directive 2001/82/EC (abridged application – generic (57 mg) and hybrid (25 mg, 100 mg and 225 mg)).

Benefit assessment

Direct therapeutic benefit

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, route of administration and dosing interval as recommended in the marketing authorisation of the reference product. The product is indicated for dogs for the relief of pain and inflammation associated with osteoarthritis, and for the relief of post-operative pain and inflammation associated with soft-tissue, orthopaedic and dental surgery.

Additional benefits

The product increases the range of available treatment possibilities for lower and higher weight categories of target animals by presenting additional strengths of tablets (25, 100 and 225 mg).

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 product should have a satisfactory and uniform performance in clinical use.

Safety:

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal:

Coxatab is not expected to pose a risk for the target animals when used according to the SPC recommendations. The main reported adverse reactions stated in SPC include renal and/or hepatic disorders and nervous system disorders. As with other NSAIDs, serious adverse effects can occur and, in very rare cases, may be fatal. The potential for mild and transient adverse effects such as emesis and diarrhoea cannot be excluded.

Risk for the user:

The safety profile of the proposed product is expected to be the same as that of the reference product and hence no additional user risk assessment concerns arise. The user safety for this product is acceptable when used according to the SPC recommendations.

Risk for the environment:

Coxatab is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, the user and the environment and to provide advice on how to prevent or reduce these risks.

User safety:

The risk mitigation measures for inclusion in section 4.5. ii) of the SPC reflect those accepted for the reference product.

Environmental safety:

Standard advice on waste disposal is included in the package leaflet.

Evaluation of the benefit-risk balance

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. It is expected to be well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended. Appropriate 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 Veterinary Medicinal Products (CVMP) concluded that the application for Coxatab 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.