07 October 2021
EMA/576208/2021
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Apoquel (EMEA/V/C/002688/X/0019)

INN: oclacitinib maleate

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

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Introduction

The applicant Zoetis Belgium SA submitted on 2 October 2020 an application for an extension to the marketing authorisation for Apoquel to the European Medicines Agency (The Agency) in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I thereof (extensions).

Apoquel film-coated tablets are authorised for oral use in dogs and contain the Janus kinase (JAK) inhibitor oclacitinib maleate as active substance. They are authorised for use in the Union with the following indications: "Treatment of pruritus associated with allergic dermatitis in dogs. Treatment of clinical manifestations of atopic dermatitis in dogs."

Apoquel film-coated tablets contain 3.6, 5.4 or 16 mg oclacitinib maleate and each strength is presented in packs of 20, 50 or 100 tablets.

This extension application pertains to a new pharmaceutical form (chewable tablets) for oral use in dogs, for the same indications as already authorised.

The rapporteur appointed is Rory Breathnach and the co-rapporteur is Niels Christian Kyvsgaard.

The dossier has been submitted in line with the requirements for submissions in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I thereof (extensions).

On 7 October 2021, the CVMP adopted an opinion and CVMP assessment report.

On 13 December 2021, the European Commission adopted a Commission Decision approving the extension to the marketing authorisation for Apoquel.

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 May 2018) 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

Batch release within the EU takes place at Zoetis Belgium SA, Louvain-la-Neuve, Belgium, which holds a manufacturing authorisation issued by the Competent Authority in Belgium.

A GMP declaration for the active substance manufacturing sites was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on on-site audits performed in the past 3 years.

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 are in line with legal requirements.

Part 2 - Quality

Composition

The finished product is presented as chewable tablets containing 3.6 mg, 5.4 mg and 16 mg of oclacitinib (as oclacitinib maleate), respectively, as the active substance, i.e. the same strengths as already authorised for the film-coated tablets. The chewable tablets are light to dark brown-coloured, elongated pentagon-shaped, mottled tablets with score lines on both sides, and are debossed in one of the faces based on corresponding strength: "S S" for 3.6 mg, "M M" for 5.4 mg and "L L" for 16 mg.

The other ingredients differ from the already authorised ones and are: pork liver powder, crospovidone Type A, sodium starch glycolate Type A, glycerol monostearate 40-55 Type II, macrogol 3350, glycerol, sodium chloride, xanthan gum, brewer's yeast dried, colloidal anhydrous silica and magnesium stearate.

Containers

Tablets are packaged in an aluminium/PVC/Aclar blister, in an outer carton. The aluminium foil and Aclar blister comply with the relevant EU requirements. The container-closure system is widely used for tablet dosage forms.

Each blister contains 10 chewable tablets with pack sizes of 20 or 100 tablets per carton.

Development pharmaceutics

The active substance oclacitinib maleate is approved for use in the manufacture of Apoquel film-coated tablets, which are centrally authorised (EU/2/13/154/001-018). This extension application is a new pharmaceutical form (chewable tablets) for oral use in dogs. In order to demonstrate essential similarity between the new chewable tablet formulation and the approved film-coated tablet, the applicant has submitted a bioequivalence study (see part 4 for details).

The chewable tablets contain the same quantitative amount of the active substance (oclacitinib maleate) as the film-coated tablets, but there are significant differences in the excipients used in both formulations. The development of the chewable tablet focussed on designing a stable, divisible, palatable, immediate-release formulation using a common blend and a dose-proportionate weight for all three strengths (3.6 mg, 5.4 mg and 16 mg). The physico-chemical characteristics of the active substance established during the development of Apoquel film-coated tablets were taken into account in the development of the chewable tablet formulation. All excipients are well known pharmaceutical ingredients, and their quality is compliant with European Pharmacopoeia (Ph. Eur.) standards, with the exception of pork liver powder and dried brewer's yeast. There are no novel excipients used in the finished chewable tablet formulation. The list of excipients is included in section 6.1 of the SPC.

Derivation of the formulation is logical and well described in the dossier, and the formulation components are commonly used in this dosage form. The function of each excipient is clearly detailed, and their selection was based on experience with the development and manufacturing of other drug products as

well as drug-excipient compatibility study results. Product with the final proposed commercial formulation was used for pivotal bioequivalence/pharmacokinetic and palatability studies as well as in the registration stability studies.

Investigation of the dissolution test is described, and dissolution profiles were generated for all the three strengths of oclacitinib chewable tablets in 0.1N HCl, acetate buffer (pH 4.5) and phosphate buffer (pH 6.8) media. The chosen dissolution method is in line with the requirements of Ph. Eur. 2.9.3, and has been demonstrated to be discriminatory. The three chewable tablet strengths showed similar dissolution profiles to each other and to the bio-batch used in bioequivalence studies consistent with dissolution profiles for an immediate release dosage form.

The manufacture of oclacitinib chewable tablets utilizes conventional pharmaceutical equipment and follows a standard pharmaceutical manufacturing process. The manufacturing development and optimisation are well described.

Method of manufacture

The manufacturing process is a standard granulation process. The manufacture of the chewable tablets involves granulation, fluid bed processing, blending and compression steps. The manufacture of oclacitinib chewable tablets utilizes conventional pharmaceutical equipment and follows a standard pharmaceutical manufacturing process. A detailed description of the manufacturing process and flow chart have been provided. In addition, a detailed listing of the in-process controls and process parameters is provided along with confirmation that changes to the in-process controls will be registered by way of the appropriate variation. In accordance with the "Guideline on process validation for finished products — information and data to be provided in regulatory submissions" (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1), it is accepted that full scale validation will be performed post-authorisation. An acceptable process validation protocol is provided. All in-process controls and process parameters are detailed in the protocol and ranges are proposed for mixing times, speeds, screen sizes etc.

Control of starting materials

Active substance

The active substance oclacitinib maleate is not monographed in the Ph. Eur. and data on the active substance is provided in part II.C.1 of the dossier. The INN for the active substance is oclacitinib maleate. The active substance has a non-chiral molecular structure, due to the presence of a plane of symmetry. The active substance may exist in 3 crystalline forms, i.e. forms A, B and C.

The manufacturing process is a chemical synthesis followed by formation of the maleate salt. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are satisfactory.

The characterisation of the active substance and its impurities are in accordance with the "Guideline on the chemistry of active substances for veterinary medicinal products" (EMA/CVMP/QWP/707366/2017). Potential and actual impurities were well characterised and discussed with regards to their origin. The active substance specification includes tests for appearance, identity (IR, HPLC, XRPD), assay (HPLC), impurities (HPLC), maleic acid (HPLC), water content (Ph. Eur.), sulfated ash (Ph. Eur.), residual solvents (GC), heavy metals (Ph. Eur.) and particle size distribution (laser diffraction). The analytical methods

used have been adequately described and validated in line with VICH GL1 and 2. Satisfactory information regarding the reference standards used for assay and impurities testing is available.

Batch analysis data has been provided for eight batches of the active substance, of which the final three were manufactured using the proposed manufacturing process and crystalline form. The results comply with the proposed specifications and are comparable between the batches.

Currently a retest period of 3 years is approved for the active substance. The active substance information is the same as that approved for the authorised product, Apoquel film-coated tablets, including all approved variations.

Excipients

The excipients are well known pharmaceutical ingredients and their quality is compliant with their respective Ph. Eur. monographs, with the exception of pork liver powder and brewer's yeast, which are not monographed. Additional test and limits for the relevant functionality-related characteristics have been included in the specifications for the pharmacopoeial excipients. There are no novel excipients used in the finished product formulation. A satisfactory specification is provided for the non-compendial excipients pork liver powder and brewer's yeast.

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

Only the pork liver powder contains materials of animal origin. Data has been presented to give reassurance on TSE safety, and a declaration that the porcine liver is sourced from animals fit for human consumption is provided.

A viral safety risk assessment in line with Ph. Eur. 5.1.7 "Viral Safety" for this animal-derived flavouring material is provided for the pork liver powder.

Control tests on the finished product

The finished product release specification controls relevant parameters for the dosage form in accordance with VICH GL39. Parameters on the specification are: appearance, identification of the active substance (HPLC and UV-diode array), assay (HPLC), uniformity of dosage units (Ph. Eur.), degradation products (HPLC), dissolution (Ph. Eur.), water (Ph. Eur.), friability, hardness and microbiological testing. Data has been provided to support the proposed limits for dissolution, which have been adequately justified in line with the "Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action" (EMA/CHMP/CVMP/QWP/336031/2017).

The analytical methods used have been adequately described and appropriately validated in accordance with VICH GL2. The test method and validation for the microbiological tests are provided and are satisfactory.

Batch analysis results are provided for nine pilot-scale bulk batches of product, yielding three batches of each strength. The results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Satisfactory information regarding the reference standard used for assay testing has been presented.

Stability

Stability data is provided for three pilot scale batches of each strength, subjected to accelerated (40 °C/ 75% RH), intermediate (30 °C/ 75% RH; higher RH to support global submission) and long-term conditions (25 °C/ 60% RH). The batches of product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, degradation products, dissolution, water content and microbiological quality. The analytical procedures used are stability-indicating. All results are in compliance with the specification, with the level of active substance generally stable for all three tablet strengths of the product at long-term conditions and no increases in degradation products. Increasing trends in water content are noted with changes in temperature and no effect on product quality. The applicant has presented statistical analysis of the stability data up to 18 months for the parameters assay and water content for each of the three tablet strengths at 25 °C/60% RH and 30 °C/60% RH. Extrapolation of the 18-month data to allow a shelf life of 24 months as proposed by the applicant is therefore considered appropriate. Inclusion of the storage precaution to store in the original package to protect from moisture is acceptable.

A photostability study was performed for one batch of each strength in Alu-Aclar blisters in accordance with VICH GL5. The results demonstrate that the product is not sensitive to light and no related precautionary statements are therefore required on the product information.

An in-use stability study was performed for one batch of each strength in Alu-Aclar blisters in accordance with the "Note for guidance on in-use stability testing of veterinary medicinal products" (EMEA/CVMP/424/01). Samples were tested for appearance, assay, degradation products, dissolution and water content, on the initial day and on days 1 and 2. No significant changes were observed. However, advice is given in section 4.5 to administer the tablet immediately. Furthermore, in order to not encourage animal owners to retain half tablets for longer than is necessary, the sentence "Remaining tablet parts should be stored in the blister and be given at the next administration" is included in the product information.

Overall conclusions on quality

In the development pharmaceutics, the applicant provides information on the development of the formulation and the development and optimisation of the manufacturing process and dissolution method. Derivation of the formulation is logical and well described in the dossier and the formulation components are commonly used in this dosage form. The function of each excipient is clearly detailed, and optimisation of concentrations described. Physicochemical aspects relevant to the performance of the product have been investigated.

The manufacture of oclacitinib chewable tablets utilizes conventional pharmaceutical equipment and follows a standard pharmaceutical manufacturing process. A detailed description of the manufacturing process and flow chart have been provided. In accordance with the "Guideline on process validation for finished products — information and data to be provided in regulatory submissions" (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1), it is accepted that full-scale validation will be performed post-authorisation and a process validation protocol is provided.

The active substance oclacitinib maleate is not monographed in the Ph. Eur. and data on the active substance is provided in the dossier. The active substance information is the same as that approved for the authorised product, Apoquel film-coated tablets, including all approved variations. A 3-year retest period is approved for the active substance.

All of the monographed excipients comply with the relevant monographs in the Ph. Eur., with additional functionality-related tests and limits. The excipients pork liver flavour and brewer's yeast dried are not monographed in any pharmacopoeia and appropriate specifications have been provided for them. Acceptable information is available for the container-closure systems for the active substance and finished product. Data has been presented to give reassurance on TSE safety. A risk assessment relating to viral safety of the animal-derived flavouring material is provided.

The finished product release specification controls relevant parameters for the dosage form. The analytical methods and their validation are satisfactory. In terms of dosage form stability, data is provided for three pilot-scale batches of each tablet strength stored under VICH real time, intermediate and accelerated conditions. Data up to 18 months under real time conditions have been presented. All results are within specification with an increasing trend in water content observed, particularly at higher temperatures. Extrapolation of the 18-month data to allow a shelf life of 24 months as proposed by the applicant is considered acceptable. Inclusion of the storage precaution in the original package to protect from moisture is acceptable.

Part 3 – Safety

Oclacitinib maleate, a JAK inhibitor, is authorised in the EU as active substance in Apoquel film-coated tablets. This is an extension application to add a new pharmaceutical form (chewable tablets).

The application makes reference to the dossier and previous assessment of the CVMP in the context of the initial marketing authorisation application for Apoquel film-coated tablets, including conclusions drawn regarding the pharmacology and toxicology of the active substance.

Safety documentation

The proposed chewable tablets contain the same quantitative amount of active substance (oclacitinib maleate) as the film-coated tablets, although, to improve the palatability of the tablets and to make the formulation chewable, there are substantial differences with respect to excipients.

Given that this is a line extension application and that the active substance of Apoquel (oclacitinib maleate) was previously authorised in the EU as part of the marketing authorisation application for Apoquel film-coated tablets (EMEA/V/C/002688), the applicant makes reference to the initial marking authorisation application for that product for pharmacological and toxicological information and no new data were submitted. To demonstrate essential similarity in the bioavailability between the new chewable tablet formulation and the approved film-coated tablet, a new bioequivalence study and an efficacy study were provided (see part 4). This approach is acceptable.

Pharmacodynamics

The pharmacodynamic profile (mechanism of action and secondary pharmacology) of oclacitinib maleate was described in the initial marketing authorisation of Apoquel. This is an extension application and, as such, the applicant makes reference to pharmacodynamic studies included in the marketing authorisation for Apoquel film-coated tablets, which can be accepted.

Pharmacokinetics

The pharmacokinetics of oclacitinib maleate have been evaluated in laboratory animals (dogs, rats and rabbits) and studies have been provided with the initial marketing authorisation of Apoquel. This is an

extension application and, as such, the applicant makes reference to pharmacokinetic studies included in the marketing authorisation for Apoquel film-coated tablets, which can be accepted.

Toxicological studies

The toxicological profile of oclacitinib maleate was described in the initial marketing authorisation application of Apoquel film-coated tablets. It included acute oral and dermal toxicity studies in rats, repeat-dose oral toxicity studies in rats, exploratory repeat-dose oral toxicity studies and margin of safety studies in dogs, developmental toxicity studies in rats and rabbits, studies to evaluate genotoxic potential and user safety studies (acute oral and dermal toxicity studies in rats, ocular and dermal irritation studies in rabbits and a mouse local lymph node assay). Based on that assessment, the following was concluded:

Oclacitinib is of moderate hazard following acute oral exposure. Repeat dose studies in rats and dogs resulted in oclacitinib-related effects (lymphoid depletion) at all doses. However, at low doses, most effects were mild and non-progressive. The most sensitive repeat-dose toxicity study was determined to be the 90-day oral study performed in dogs, where the lowest observed adverse effect level (LOAEL) was 0.5 mg/kg bw/day based on hypocellularity of lymphoid and hematopoietic tissues. Oclacitinib was not embryolethal in rats at oral doses ≤ 5 mg/kg bw/day or in rabbits at doses ≤ 30 mg/kg bw/day, and was not teratogenic in rats at oral doses ≤ 25 mg/kg bw/day or in rabbits at doses ≤ 60 mg/kg bw/day. From the studies provided, it is considered that oclacitinib maleate is not genotoxic or mutagenic. The absence of carcinogenicity studies was justified on the basis that oclacitinib was not mutagenic or genotoxic in a standard battery of tests. There were no proliferative changes in the 90-day oral rat toxicity study and there are no structural alerts for carcinogenicity. Irritation studies with oclacitinib indicate that it is a mild or slight irritant to intact skin and corrosive to the eye. It did not elicit a skin sensitization reaction in mice.

This is an extension application and it is noted that the amount of active substance in the formulation of the chewable tablets remains unchanged from the authorised film-coated tablets. However, to make the formulation chewable and to enhance palatability, there are substantial differences with respect to excipients. Given that the toxicological properties of oclacitinib have been previously assessed during the procedure for the marketing authorisation for Apoquel film-coated tablets, no additional toxicity data relating to the active substance has been provided. This is considered acceptable.

It is noted that toxicological data relating to the new excipients has been included in the user risk assessment and that the excipients are commonly used in approved veterinary or human pharmaceutical products or are approved as food additives. They are therefore not anticipated to pose a toxicological concern at the levels used in the formulation. This is accepted.

Tolerance in the target species of animal

The tolerance in the target animal is described under part 4.

User safety

A user risk assessment has been provided and is broadly in accordance with the "CVMP guideline on user safety for pharmaceutical medicinal products" (EMA/CVMP/543/03-Rev.1).

This is an extension application and it is noted that the amount of active substance in the formulation of the chewable tablets remains unchanged from the authorised film-coated tablets, and that a substantial change in excipients to make the formulation chewable and to enhance palatability has been made. Given that the excipients are well known and are used in other veterinary medicinal products currently

authorised in the EU, it is not expected that the excipients will present a hazard to the user and their inclusion in the formulation is considered acceptable. For characterising the risk to the user, the substance of primary concern is the active substance.

Dermal studies included in the marketing authorisation dossier for the film-coated tablets indicated that oclacitinib maleate has the potential to cause mild or slight irritation to skin and it was determined to be corrosive to rabbit eyes.

The original Apoquel formulation contained a film coating that reduced the probability of user exposure to the substances in the product and thereby effectively eliminated the potential for dermal or ocular irritation. The proposed chewable tablets do not have this coating. While it can be accepted that the absence of a film coating increases the potential for dermal and ocular exposure to the active substance following handling of the product (relative to extent of exposure associated with handling of the film-coated tablets), the CVMP is of the opinion that the possible extent of user exposure during handling/normal use of the product remains limited given the proposed solid dose form of the chewable tablet. Considering that the changes in formulation are not expected to result in a meaningful change to the extent of user exposure via the dermal or ocular routes, it can be accepted that the proposed risk mitigation measures for inclusion in the product literature (which reflect those already accepted for the approved film-coated tablet formulation) are appropriate. Any risk associated with dermal exposure will be mitigated by the proposed warning to wash hands after administration of the product.

Notwithstanding the fact that the tablets are divisible, the potential risk to the user via the inhalation route is negligible. It is noted that the authorised film-coated tablets are also divisible.

The applicant has considered a worst-case exposure scenario of accidental ingestion by a child of two 16 mg tablets which would result in an exposure of 3.2 mg/kg bw. Given that a NOAEL was not determined, the use of a LOAEL of 0.5 mg/kg bw/day derived from a repeat dose study in dogs can be accepted. It is apparent that in this exposure scenario, the resulting margin of exposure (MOE) for the active substance (oclacitinib) is below the threshold value of 100 (MOE = 0.16) and, consequently, it must be concluded that an unacceptable risk to the user arises following accidental ingestion by a child.

Given the above, it is considered appropriate that suitable risk mitigation measures are applied.

The applicant states that the product will be supplied in a robust packaging (blister packs) and that this will mitigate the risk of ingestion by a child. Although the packaging has not been certified as child-resistant, the applicant has confirmed that the proposed packaging is identical to that previously accepted for the authorised film-coated tablets.

In conclusion, the CVMP considers that the changes in formulation are not expected to result in a meaningful change to the extent of user exposure via the dermal or ocular routes. Therefore, it can be accepted that the proposed risk mitigation measures for inclusion the product literature (which reflect those already accepted for the approved film-coated tablet formulation) are appropriate. Any risk associated with dermal exposure will be mitigated by the proposed warning to wash hands after administration of product. The user safety assessment appropriately considers the risk to children associated with accidental oral exposure, and suitable wording has been included in the product literature, in addition to the proposed packing being identical to the packaging for the authorised film-coated tablets.

Environmental risk assessment

A phase I environmental risk assessment (ERA) was provided according to relevant CVMP/VICH guidelines. Given that the product is only intended for administration to individual non-food-producing animals, the environmental risk assessment may end in phase I.

It can be concluded that the product will not present an unacceptable risk for the environment when handled, administered, stored and disposed of in accordance with the recommendations proposed for inclusion in the SPC.

Overall conclusions on the safety documentation

This is an extension application and, as such, the applicant makes reference to pharmacokinetic, pharmacodynamic and toxicological studies included in the marketing authorisation for Apoquel film-coated tablets (EMEA/V/C/002688), which can be accepted. It is noted that the amount of active substance in the formulation of the chewable tablets remains unchanged from the authorised film-coated tablets. However, to make the formulation chewable and to enhance palatability, there are substantial differences with respect to excipients. To demonstrate essential similarity in the bioavailability between the new chewable tablet formulation and the approved film-coated tablet, a new bioequivalence study and an efficacy study have been included in part 4.

It is noted that toxicological data on the new excipients has been included in the user risk assessment and that the excipients are commonly used in approved veterinary or human pharmaceutical products or are approved as food additives. They are therefore not anticipated to pose a toxicological concern at the levels used in the formulation, which is accepted.

The changes in formulation are not expected to result in a meaningful change to the extent of user exposure via the dermal or ocular routes. Therefore, it can be accepted that the proposed risk mitigation measures for inclusion in the product literature (which reflect those already accepted for the approved film-coated tablet formulation) are appropriate. Any risk associated with dermal exposure will be mitigated by the proposed warning to wash hands after administration of product. The user safety assessment appropriately considers the risk to children associated with accidental oral exposure, and suitable risk mitigation information has been included in the product information.

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.

Part 4 – Efficacy

Pharmacodynamics

To describe the pharmacodynamic profile of oclacitinib maleate and given that this is an extension application, the applicant has made reference to studies that have already been submitted and assessed in the marketing authorisation for Apoquel film-coated tablets, which is acceptable. In addition, new recent literature references were provided.

Oclacitinib is a JAK inhibitor, which is a family of intracellular, non-receptor tyrosine kinases. These enzymes play a key role in allowing extracellular proteins such as cytokines to transmit signals to the nucleus of target cells to initiate biological responses. Numerous cytokines are known to activate the JAK family of enzymes, including pro-inflammatory cytokines as well as cytokines implicated in allergic responses. Based on the data presented, it appears that oclacitinib is a JAK inhibitor with limited activity against a range of cell surface receptors, ion channels, transporters, and other intracellular enzymes, and that oclacitinib can inhibit the function of a variety of cytokines dependent on JAK enzyme activity. A number of these cytokines have a role in the pathophysiology of allergic skin disease/canine atopic dermatitis.

In a study conducted to determine the role of IL-31 in canine pruritus and naturally occurring canine atopic dermatitis, canine IL-31 was detected in the majority of dogs with naturally occurring atopic dermatitis, suggesting that this cytokine may play an important role in pruritic allergic skin conditions, such as atopic dermatitis. Further, administration of canine IL-31 by intravenous, subcutaneous or intradermal routes induced pruritic behaviours in dogs.

The applicant also provided a summary of a model that had been developed using PK/PD data based on two IL-31-induced pruritus challenge studies in dogs (already assessed in the initial marketing authorisation for Apoquel film-coated tablets). In these challenge studies, pruritic behaviours were assessed for 120 minutes after the intravenous administration of oclacitinib (or a placebo) and assigned a pruritus score (the highest possible score was 120). The PK/PD modelling estimated a plasma concentration of 12.1 ± 11.8 ng/ml oclacitinib to achieve a 50% reduction in pruritus (EC_{50}).

Development of resistance

Given the nature of the product (JAK inhibitor), development of resistance is not considered relevant and therefore no assessment is required.

Pharmacokinetics

In order to bridge data from the film-coated formulation to the chewable formulation, the applicant has submitted a dataset consisting of:

- a new bioequivalence study comparing the two formulations,
- a PK/PD model calculation, and
- a new experimental efficacy study.

Bioequivalence study

The applicant performed a GLP-compliant bioequivalence study comparing the new chewable formulation (test product) with the authorised film-coated formulation (reference product). This study was performed in the United States; however, the reference product used (Apoquel film-coated tablet) was manufactured in the EU. The study was performed in accordance with VICH GL52 "Bioequivalence: blood level bioequivalence study" (EMA/CVMP/VICH/751935/2013). In the randomised, blinded, two-way cross-over study, 48 female Beagle dogs aged 12–19 months, and with a bodyweight of approximately 6–10 kg were administered a single 5.4 mg tablet of either the new chewable tablet or the authorised film-coated tablet. Animals were fasted overnight prior to dosing and fed at approximately 4 hours post dose. Blood samples for oclacitinib determination were collected 0.5 hours prior to dosing and for up to 32 hours after administration of the test or reference product. AUC, C_{max} and T_{max} were determined. Samples were stored and shipped at -60 °C for analysis.

The number and frequency of samples collected is considered sufficient given that C_{max} has been adequately characterised for both products and the $AUC_{0\text{-}t(last)}$ is at least 80% of the $AUC_{0\text{-}\infty}$. A washout period of 7 days was applied. As this was more than five times the terminal half-life of the active substance, it can be accepted that the washout period was adequate.

The dose administered (single dose of 0.5–0.9 mg/kg bw) was not in accordance with the proposed dose (single or twice daily 0.4–0.6 mg/kg bw), as each dog was administered one 5.4 mg tablet. However, given that all dogs were administered at least the minimum treatment dose (albeit some dogs were administered a higher dose than recommended) the approach used by the applicant can be accepted.

Following dosing with Apoquel film-coated tablets (T01), the mean C_{max} was 475 ng/ml (90% CI: 392–576), which occurred at a mean t_{max} of 1.2 hours (1.1–1.4 hours). Following dosing with the chewable tablet (T02), the mean C_{max} was 352 ng/mL (90% CI: 288–429), which occurred at a mean t_{max} of 1.7 hours (1.5–1.8 hours).

Overall exposure was similar between the groups with mean $AUC_{0\text{-}t(last)}$ of 3260 and 3000 ng/h/ml for T01 and T02, respectively. The mean $t_{1/2}$ values were also similar across groups at 4.35 and 4.81 hours for T01 and T02, respectively.

$AUC_{0\text{-}t(last)}$ but not C_{max} met the criteria for bioequivalence of the 90% CI for the geometric mean ratios being contained within 0.80 and 1.25. The geometric mean ratio for $AUC_{0\text{-}t(last)}$ was 0.923, with a 90% CI of 0.884–0.963. The geometric mean ratio for C_{max} was 0.740, with 90% confidence interval of 0.678–0.807.

Overall, it can be accepted that this study was generally well conducted, and the results can be reliably interpreted.

Based on the findings of this study, bioequivalence between the candidate product (chewable tablet) and reference product (authorised film-coated tablet) for the overall exposure (AUC) can be accepted.

However, bioequivalence for the parameter C_{max} between the candidate and reference product was not confirmed in this study. The significance of this in terms of the potential for reduced efficacy of the candidate product and its clinical relevance was considered by the applicant using a PK/PD calculation and a pre-clinical efficacy model, the results of which are both described below.

In accordance with the "CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products" (EMA/CVMP/016/2000-Rev.3-corr.*),* the applicant has provided information on the dissolution profiles of all three tablet strengths in three different buffers (pH 1.2, 4.5 and 7.5). It can be accepted that the applicant has satisfactorily demonstrated similarity of dissolution profiles for the three tablet strengths at pH 1.2, 4.5 and 7.5, thus allowing for the extrapolation of in vivo bioequivalence data from the 5.4 mg strength tablet to the 3.6 and 16 mg tablet strengths.

PK-PD model

In order to demonstrate that the lower C_{max} observed for the chewable tablet formulation in the bioequivalence study would have minimal to no clinically relevant effect on the efficacy of the chewable tablets, the applicant applied the results from the bioequivalence study to the PK/PD model that was developed as part of dose justification for the authorisation of Apoquel film-coated tablets.. The applicant used the EC_{50} value and the C_{max} observed in the bioequivalence study for each formulation to estimate a percentage pruritus score, which resulted in predicted percentage pruritus scores of 6.48% for the film-coated and 7.32% for chewable tablet.

The applicant therefore concluded that the PK/PD model indicated that the difference in C_{max} between formulations observed in the bioequivalence study (lower C_{max} observed when compared with the C_{max} observed for the film-coated tablets) would only result in minimal differences in efficacy.

The predictions from the PK/PD modelling are noted and are accepted as being generally supportive in demonstrating that the difference between formulations with respect to the C_{max} is of limited clinical relevance. In addition, the applicant has provided PK/PD modelling for multiple dosing that simulates the PK profile of the two tablet formulations at steady state and further supports that the two formulations will have similar effect.

Experimental efficacy study

To further support the claim of essential similarity between the chewable tablet product and authorised film-coated product, and to demonstrate that a lower C_{max} will not affect clinical efficacy, the applicant has provided an experimental efficacy study evaluating the chewable tablets at a single oral dose of 0.4 mg/kg bw in a canine model of IL-31-induced pruritus.

In this study, the anti-pruritic activity from the proposed chewable tablet and the approved film-coated tablet was assessed using an IL-31-induced pruritus model. Twenty-one Beagle dogs were included in the randomised study, with seven dogs allocated to each of three groups. The first group (T01) were administered a negative control (placebo), the second group (T02) were administered the approved film-coated tablet and the third group (T03) were administered the proposed chewable tablet at a single dose proposed in the SPC (0.4–0.6 mg/kg bw). To establish a baseline pruritis score, each animal was administered an IL-31 challenge (2.5 µg/kg bw) intravenously to induce pruritus on study day -14. The IL-31 challenge was repeated approximately 45 minutes after dosing with the assigned test article on day 0. Animals were observed for pruritic behaviour for a 120-minute period beginning 1 hour after dosing with the test article. Displays of pruritic behaviour were used to determine a pruritus score. Blood samples were collected to determine the plasma levels of oclacitinib three hours after administration of the test product.

Noting that the primary purpose of this study was to investigate the clinical relevance of the difference in C_{max} observed in the bioequivalence study, the assessment of reduction in pruritis score over a period of two hours, beginning 15 minutes after the IL-31 challenge, is considered appropriate. Thereafter, either up to 12 hours in the case of initial treatment or 24 hours in the case of maintenance therapy, it is expected that the products will behave similarly given the comparable AUC.

Over the full 2-hour observation period, both study groups administered the authorised film-coated tablets and the chewable tablets showed a significantly different total pruritus score compared with control group (p = 0.0069 and 0.0113, respectively). The control group had a mean number of minutes with pruritus of 84 (out of a possible 120) while the film-coated tablets had a mean of 27 minutes and the chewable tablets had 26 minutes. The film-coated tablets also showed a significant difference in the total scores from 0 to 1 hour (p = 0.0279) and 1 to 2 hours (p = 0.0013) compared with the negative control. For the chewable tablets group, the difference relative to placebo did not meet statistical significance for the 0 to 1-hour total score (p = 0.0696), but statistical significance was achieved during the 1 to 2-hour period (p = 0.0020) and for the full 2-hour observation period (as stated above). For the 0 to 1-hour time period, the chewable tablets had a mean total number of minutes of pruritus of 15 while the control mean was 36, i.e. a 58% difference.

The average mean plasma concentration of oclacitinib after three hours for the groups administered the film-coated and the chewable tablets were 154.74 ng/ml and 236.1 ng/ml, respectively.

No information comparing the rate of onset of anti-pruritic activity between the film-coated and chewable tablet formulations has been included in the study report. However, the results demonstrate that there was a reduction in pruritus within the first hour for both tablet formulations when compared to the control with a mean pruritus score of 12 and 15 for the film-coated tablets and chewable tablets, respectively, versus 36 for the placebo. A statistically significant lower total pruritus score was observed for both formulations when compared with the negative control over the entire 2-hour observation period.

Conclusions:

Based on the findings of the bioequivalence study, bioequivalence for the overall exposure (AUC) between the chewable tablet and the approved film-coated tablet formulations was demonstrated. However,

bioequivalence for C_{max} was not demonstrated between the chewable tablet and the approved film-coated tablet formulation. The applicant did provide further information in the form of a PK/PD model and an experimental efficacy study demonstrating that the difference in C_{max} would not be clinically relevant.

Taking into consideration the overall data package provided by the applicant, a comparable efficacy between the new chewable tablet formulation and the approved film-coated formulation can be accepted.

Dose justification

The recommended initial dose is 0.4 to 0.6 mg oclacitinib/kg bw, administered orally, twice daily for up to 14 days. For maintenance therapy, the same dose should then be administered only once a day. The proposed dose for the chewable tablet form is the same as that approved for the authorised film-coated tablets. Therefore, no new dose justification studies were provided. This approach is acceptable.

Target animal tolerance

This is an extension application and the amount of active substance in the formulation of the chewable tablets remains unchanged from the authorised film-coated tablets. However, to make the formulation chewable and to enhance palatability there are substantial differences with respect to excipients. The toxicological properties of the active substance oclacitinib have been previously assessed during the procedure for the marketing authorisation for Apoquel film-coated tablets and, when considered with the results from the bioequivalence study, the applicant states that no additional data are considered necessary. Consequently, it is accepted that no new target animal safety data are considered necessary for the active substance.

Data relating to the new excipients (pork liver powder, crospovidone, glycerol monostearate, polyethylene glycol, glycerine, sodium chloride, xanthan gum, brewer's yeast and colloidal silicon dioxide) have been provided by the applicant. The excipients are commonly used in approved veterinary or human medicinal products, or are approved as food additives and, therefore, are not anticipated to pose a safety concern to the target species at the levels used in the formulation.

Clinical studies

Palatability

In support of the palatability/acceptability of the candidate formulation, the applicant has provided the results of three studies.

Pivotal palatability study in kennel dogs

In order to demonstrate the acceptability of the tablets with the new flavouring, the applicant conducted a laboratory-based palatability study in accordance with the relevant CVMP guideline (EMA/CVMP/EWP/206024/2011). In this study, 25 dogs were offered the test product (chewable tablet) twice for seven days at the recommended dose (0.4–0.6 mg/kg bw). Voluntary acceptance was assessed over two minutes, in the first instance from the floor or in a bowl, then from the hand. From 346 acceptance tests there were 273 successful administrations resulting in an overall voluntary acceptance rate of 78.9%. In the 273 tests where the test product was fully consumed, the mean time for uptake was 15 seconds. On the majority of the 273 occasions where the test product was fully consumed, this occurred from the bowl/floor (244 tests; 83.8%) and in 29 instances (10.0%) from the hand. The

applicant concluded that there were no treatment-related adverse events observed in this study. However, it is noted that diarrhoea was reported in two dogs. Given that section 4.6 of the proposed SPC included diarrhoea as a possible common adverse event, the possibility of this adverse event being treatment-related cannot be excluded. In accordance with the "CVMP guideline on the demonstration of palatability of veterinary medicinal products" (EMA/CVMP/EWP/206024/2011), to accept a claim of palatability, the overall voluntary acceptance rates should at least reach the threshold of 80% in dogs in a group of at least 25 animals. Although initially 25 animals were enrolled in the study, only 24 dogs completed the study and the overall voluntary acceptance rate was calculated to be 78.9%. Consequently, palatability of the candidate formulation has not been demonstrated in this study in accordance with the aforementioned CVMP guideline.

Field palatability study in individual dogs – USA

The second study included in support of the palatability claim was a field study (A163C-US-A40) conducted in ten veterinary practices in the United States in accordance with FDA guidelines. 121 client-owned dogs of various breeds, ages and bodyweights were included in the study, which can be accepted as being sufficiently representative of the target population. The dogs were administered the product twice daily, which is in accordance with the SPC for the recommended initial dose. The entire dose was offered by placing the test product in an empty food bowl or in the palm of the owner's hand. The owners observed the dogs over a period of five minutes to assess whether the total dose was consumed. Any unconsumed dose was administered by assisted administration (i.e. with food or a treat).

The entire dose was fully consumed within five minutes in 91.6% of all 1673 tests conducted and the full consumption rate was similar across all 14 dosings (range of 89.9–93.3%). Although the overall voluntary acceptance rate (primary efficacy endpoint) was calculated to be 91.6%, which is above the threshold of 80 % stated in the relevant CVMP guideline (EMA/CVMP/EWP/206024/2011), the study, as conducted, was not strictly in accordance with this guidance. For example, the test product was offered either in a bowl or by hand for a total of five minutes, which is longer than the maximum time offering of two minutes in the CVMP guideline. Furthermore, it would appear that, when the candidate product was expelled or regurgitated within the five-minute observation time and the owner re-offered it, this was recorded as acceptance of the product if the dog subsequently fully consumed it.

Therefore, whilst the applicant concluded an overall voluntary acceptance rate of 91.6% in this study, it is not accepted that palatability of the candidate formulation has been demonstrated in this study in accordance with the aforementioned CVMP guideline.

Product development study in kennel dogs

The third study in support of the palatability claim was conducted during the formulation development phase of the candidate product to assess the voluntary acceptance and consumption of three different formulations. 96 dogs carried out four series of voluntary acceptance tests on three consecutive days with a four-day wash-out period between each series. Each dog was offered one single tablet of one of three formulations containing 5.4 mg oclacitinib or placebo (flavour excipients only), once daily. One of the formulations included was identical to the proposed final formulation of the chewable tablets. The tablet was placed in a bowl and the bowl was positioned inside the animal's pen. A timer was started when the dog was allowed access to the IVP after it had been positioned in the pen. If the product was not taken into the mouth or was not fully consumed after 60 seconds, the remaining tablet was offered to the dog by a technician from the hand for a further 60 seconds. If the dog had not taken the product into its mouth or consumption was not complete within the two minutes of offering time, the test was terminated. The test product with the proposed final formulation of the chewable tablets was fully

consumed within two minutes in 84.8% of all 283 tests conducted in up to 95 dogs. The full consumption rate was similar across all three test days (85.3%, 85.1% and 84.0% on the first, second and third test day, respectively), indicating that no test aversion occurred with repeated tests. The overall full consumption was similar to a placebo (82.2%), indicating that the addition of oclacitinib to the formulation had no negative impact on the palatability of the product.

The overall voluntary acceptance rate for the proposed final formulation was 84.8%, which was above the threshold of 80% as stated in the relevant CVMP guideline (EMA/CVMP/EWP/206024/2011). However, dogs were not administered the dose in accordance with the proposed SPC (0.4–0.6 mg/kg bw) but were administered a single 5.4 mg tablet for any sized dog, and some divergences from the above-mentioned CVMP guideline on palatability were noted (e.g. the study duration of three days is shorter than the seven days advised in the guideline). However, the number of animals included in the study (96) was well above the 50 recommended in the guideline to establish palatability, and, overall, it can be accepted that, from this study, 84.8% of dogs voluntarily accepted the chewable tablet formulation within two minutes, and, as such, the results from this study can be considered as generally supportive for the claim of palatability.

The applicant has proposed wording for inclusion of the SPC "Apoquel tablets are chewable, palatable and readily consumed by the majority of dogs", which is acceptable.

Conclusions:

The overall voluntary acceptance result from the pivotal palatability study was 78.9%, i.e. just below the 80% threshold stated in the guideline. The palatability field study conducted in the United States appears to be a well conducted study that included 121 client owned dogs and resulted in a voluntary acceptance rate of 91.6%, albeit the test product was offered for five minutes (not two as per the relevant CVMP guideline). The third product development study, although not conducted fully in accordance with relevant guidance, did include a voluntary acceptance rate that was in accordance with the CVMP palatability guideline, resulting in 84.8% of dogs voluntarily accepting the product over the requisite two minutes. Although this study was shorter than recommended in the guideline (three days instead of seven), it would appear from the individual daily results that no test aversion occurred within the repeated tests.

Taking into consideration the information provided from all three palatability studies, the data provided is overall sufficient to support the claim of the palatability of the product, and the wording proposed in section 4.9 of the SPC can be accepted.

Overall conclusion on efficacy

Bioequivalence: To bridge data from the film-coated formulation to the chewable formulation, the applicant performed a bioequivalence study. This study was GLP-compliant and well conducted, such that the results can be reliably interpreted. Based on the findings of this study, bioequivalence was demonstrated for the overall exposure $AUC_{0\text{-}t(last)}$ between the reference and candidate products with the geometric mean ratio for the $AUC_{0\text{-}t(last)}$ of 0.923 and a 90% confidence interval within the acceptance range of 0.80 to 1.25. However, as the geometric mean ratio for the C_{max} with 90% confidence interval was not within the acceptance range of 0.80 to 1.25, the applicant submitted two additional studies as outlined below.

PK/PD modelling: Using the PK/PD model developed for the initial formulation, the applicant concluded that the differences in C_{max} between the film-coated and the chewable tablet observed in the bioequivalence study was expected to result in a minimal difference in efficacy. Whilst the predictions from the PK/PD modelling were noted, to allow for an overall conclusion on efficacy to be made, the

applicant further justified the relative influence changes in C_{max} and AUC have on the predicted efficacy of oclacitinib using efficacy studies. In addition, the applicant provided PK/PD modelling for multiple dosing that simulates the PK profile of the two tablet formulations at steady state and further supports that the two formulations will have similar effect.

IL-31 experimental study: To further support the claim of essential similarity between the chewable tablet product and authorised film-coated product, the applicant provided an experimental efficacy study using a canine model of IL-31-induced pruritus. A statistically significant lower total pruritus score was observed for both formulations when compared with the negative control over the entire 2-hour observation period. In accordance with the "CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products" (EMA/CVMP/016/2000-Rev.3*),* the applicant has provided information on the dissolution profiles of all three tablet strengths in three different buffers (pH 1.2, 4.5 and 7.5). It can be accepted that the applicant has satisfactorily demonstrated similarity of dissolution profiles for the three tablet strengths at pH 1.2, 4.5 and 7.5, thus allowing for the extrapolation of in vivo bioequivalence data from the 5.4 mg strength tablet to the 3.6 and 16 mg tablet strengths.

Taking into consideration the overall data package provided by the applicant, it can be accepted that a comparable efficacy between the proposed chewable tablet formulation and the approved film-coated formulation has been demonstrated.

Target animal safety: The toxicological properties of the active substance oclacitinib have been previously assessed during the procedure for the marketing authorisation for Apoquel film-coated tablets. Data relating to the new excipients have been provided by the applicant. The excipients are commonly used in approved veterinary or human pharmaceutical products, or are approved as food additives and, therefore, are not anticipated to pose a safety concern to the target species at the levels used in the formulation.

Palatability: The overall voluntary acceptance result from the pivotal palatability study were, at 78.9%, just below the 80% threshold stated in the relevant CVMP guideline. The palatability field study conducted in the United States appears to be a well conducted study that included 121 client-owned dogs and resulted in a voluntary acceptance rate of 91.6%, albeit the test product was offered for five minutes (not two as per the CVMP guideline). The third product development study, although not conducted fully in accordance with relevant guidance, did include a voluntary acceptance study resulting in 84.8% of dogs voluntarily accepting the product over the requisite two minutes. Although this study was shorter than recommended in the relevant CVMP guideline (three days instead of seven), it would appear from the individual daily results that no test aversion occurred within the repeated tests.

Taking into consideration the information provided from all three palatability studies, the data provided is sufficient overall to support the claim of the palatability of the product. Thus, the wording proposed in section 4.9 of the SPC can be accepted.

Part 5 – Benefit-risk assessment

Introduction

Apoquel is already authorised as film-coated tablets (active substance: oclacitinib as oclacitinib maleate) in three different strengths (3.6, 5.4 and 16 mg oclacitinib) in packs containing 20, 50 or 100 tablets of each strength, for the treatment of pruritus associated with allergic dermatitis or for the treatment of clinical manifestations of atopic dermatitis in dogs.

This extension application is for a new pharmaceutical form, chewable tablets, at the same strengths and for the same indications as the already authorised film-coated tablets.

The dossier has been submitted in line with the requirements for submissions in accordance with Article 19 of Commission Regulation (EC) 1234/2008 and Annex I thereof (extensions).

Benefit assessment

Direct therapeutic benefit

The proposed benefit of the product is its efficacy in the treatment of pruritus associated with allergic dermatitis and the clinical manifestations of atopic dermatitis in dogs.

The evidence for the direct therapeutic benefit is considered established on the basis of bioequivalence to the reference product (Apoquel film-coated tablets) when administered at the same dose, route of administration and dosing interval as recommended in the marketing authorisation for the reference product.

Additional benefits

As the new formulation is chewable and palatable, a potential additional benefit of this product is improved animal acceptance and facilitating increased administration compliance when compared with the authorised film-coated tablets.

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:

Risks for the target animal:

The safety of oclacitinib maleate in dogs was accepted for the authorised product Apoquel film-coated tablets. The new excipients included in the chewable tablet product are not anticipated to pose a safety concern to the target species at the levels used in the formulation.

Risk for the user:

User safety risks have been identified, mainly the risks associated with exposure in children. These risks are mitigated by information included in the product information.

Risk for the environment:

The product is not expected to pose a risk for the environment when used according to the SPC recommendations.

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, user, the environment, and to provide advice on how to prevent or reduce these risks.

It is recommended that the marketing authorisation holder monitors user safety under the signal management process and includes any findings in the relevant annual statement in accordance with Article 81(1) and (2) of Regulation (EU) 2019/6.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the same indications as already authorised, i.e. "Treatment of pruritus associated with allergic dermatitis in dogs" and "Treatment of clinical manifestations of atopic dermatitis in dogs", and the CVMP accepted the indications as proposed by the applicant.

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 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.

Based on the data presented, the overall benefit-risk is considered positive.

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 Apoquel chewable tablets is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation [EC] No 1234/2008 in conjunction with Directive 2001/82/EC).

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