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Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for APOQUEL (EMEA/V/C/002688/0000)

International non-proprietary name: 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 Pfizer Animal Health S.A. submitted on 26 July 2012 an application for marketing authorisation to the European Medicines Agency (The Agency) for APOQUEL, through the centralised procedure falling within Article 3(2)(a) of Regulation (EC) No 726/2004 (new active substance). During the procedure the applicant changed to Zoetis Belgium S.A.

The eligibility to the centralised procedure was confirmed by the CVMP on 12 January 2012 falling under Article 3(2)(a) of Regulation (EC) No 726/2004 as APOQUEL contains a new active substance which was not authorised in the Community on the date of entry into force of the Regulation.

APOQUEL film-coated tablets contain oclacitinib (as oclacitinib maleate) as the active substance. There are three different strengths of the (film-coated) tablets, containing 3.6 mg, 5.4 mg and 16 mg oclacitinib (as the maleate salt), and each is contained in blister packs (polychlorotrifluoroethylene (PCTFE)/polyvinylchloride (PVC)/aluminium) which are supplied in outer cartons containing 20 or 100 tablets. The route of administration is oral use. The target species is dogs. The product is indicated for the treatment of pruritus associated with allergic dermatitis in dogs and the treatment of clinical manifestations of atopic dermatitis in dogs.

The dossier was submitted in line with the requirements under Article 12(3) of Directive 2001/82/EC.

The CVMP adopted an opinion and CVMP assessment report on 18 July 2013.

On 12 September 2013, the European Commission adopted a Commission Decision for this application.

Scientific advice

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant provided a detailed description of the pharmacovigilance system 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

APOQUEL tablets are manufactured, packaged and batches released by Pfizer Italia s.r.l., Italy.

A GMP certificate for the site was provided which confirms the date of last inspection and that the site is authorised for the manufacture and batch release of such tablet formulations.

A satisfactory GMP declaration has been provided for the active substance manufacturing site.

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 dosage form manufacturing sites have been satisfactorily established.

Part 2 - Quality

Composition

APOQUEL tablets are white to off-white, film-coated, caplet shaped tablets with a single score line on both sides. The tablets contain oclacitinib (as oclacitinib maleate) as the active substance. There are three different strengths of the tablets containing 3.6 mg, 5.4 mg or 16 mg oclacitinib. The tablets are imprinted on both sides with 'AQ' and the different sizes are also imprinted on both sides with a dose descriptor, 'S, M or L' for the 3.6 mg, 5.4 mg and 16 mg tablets respectively. The excipients used in the formulation are microcrystalline cellulose, lactose monohydrate, sodium starch glycollate and magnesium stearate. All are pharmacopoeial grade and all are commonly used in tablet formulations. The film coat is an aqueous based film coating system which is composed of lactose monohydrate, hypromellose, titanium dioxide and macrogol/polyethylene glycol 400. The coating material is a standard one, commonly used in tablet manufacture.

Container

The tablets are packaged in blister packs (PCTFE/PVC/aluminium) which are supplied in outer cardboard cartons containing 20 or 100 tablets.

Development pharmaceutics

The formulation is typical for an immediate release film-coated tablet where the core tablet is prepared by a direct compression manufacturing process. The three tablet strengths are manufactured from a common blend. Extensive formulation development is described in the dossier, from active substance properties to excipient selection and optimisation, and manufacturing process optimisation.

The active substance is highly soluble at low pH with high bioavailability and absorption within the low pH upper gastrointestinal tract. The maleate salt of the active substance is used in the formulation and this exists in several crystalline forms. The commercial form of the active substance selected was justified by studies. The active substance specification includes a limit for water content which aids in the control of the selected crystalline form, and the data supplied justify this.

Details of the different active substance batches/forms used in the various clinical studies are provided, and bioequivalence of the different forms of the active substance has been demonstrated.

Selection of the excipients used in the formulation was based on compatibility studies with the active substance and other excipients. Different formulations were then evaluated, based on dissolution profiles and stability, before selection of the final formulation.

The development of the manufacturing process includes a design of experiments approach for optimisation of the screening/blending and lubrication steps. The compression and coating processes were developed using conventional approaches. The design of experiments was generally well designed and the supporting data largely satisfactory. However, it is not intended to apply a design space. Fixed values are to be used for screen size, blender speed, blending time and lubrication time and should changes be required to them in the future, appropriate variations will require to be submitted. The only parameter of the manufacturing process for which a range is registered is blender occupancy, which may vary within the stated validated range depending on batch size. This is acceptable.

The tablets are intended to be broken in half to facilitate dosing, and data demonstrating compliance with the European Pharmacopoeia (Ph. Eur.) monograph for tablets, subdivision of tablets, have been provided.

Method of manufacture

All three tablet strengths are manufactured from a common blend with compression of different tablet weights to produce the 3 different strengths. A description of the manufacturing process is provided. The process utilises standard manufacturing techniques and consists of blending, lubrication with magnesium stearate, tabletting, film coating and packaging. The level of detail provided in this section of the dossier is sufficient and adequate in-process controls are described.

Control of starting materials

Active substance

Oclacitinib maleate is the active substance used in oclacitinib maleate film-coated tablets. The manufacturing process is a chemical synthesis followed by formation of the maleate salt. The justification for the designation of the starting materials is considered appropriate. Appropriate specifications for the starting materials are provided and are satisfactorily justified. Specifications for other materials used in the process are also satisfactory. The development of the manufacturing process for the active substance is described and the level of detail provided is sufficient. This description of the manufacturing process includes, where relevant, details of reaction times, temperatures, volumes, filtration steps, seeding etc. Details of the processes used for collecting, washing and drying of solids at each step are also specified. Acceptable ranges for these parameters that will allow sufficient manufacturing flexibility for the process are specified.

A comprehensive review of the origin and control of all potential impurities arising in the process is provided and is satisfactory.

The specification for the active substance controls critical parameters for the quality of the active substance. Assay limits are set taking into account results from batches manufactured according to the proposed manufacturing process, with an allowance for manufacturing variability. One impurity in the active substance is qualified above the VICH qualification threshold specified in VICH guideline GL10 on impurities in new veterinary drug substances (CVMP/VICH/837/99-Rev.1). A limit of 1.0% is applied to this impurity based on the toxicological data provided and the manufacturing capability of the process.

Analytical methods and their validation are described for analysis of the assay, purity and maleic acid. Other test methods are standard pharmacopoeial methods.

Active substance stability studies have been conducted on three batches in accordance with the VICH guideline GL3 on stability testing of new veterinary drug substances and medicinal products (EMEA/CVMP/VICH/899/99-Rev.1). Results of the tests demonstrate the active substance to be extremely stable with no adverse trends in any of the parameters investigated. The proposed retest period of 2 years is supported.

Excipients

All excipients of the tablet core comply with the relevant monographs in the current Ph. Eur. The coating material is the only non-pharmacopoeial excipient used in the product, but its individual components comply with their respective Ph. Eur. monographs. A specification is provided for the coating material and the tests are conducted according to Ph. Eur. methodology and validation data are therefore not required.

Container closure system

Active substance

Oclacitinib maleate is packaged in sealed, low density polyethylene (LDPE) bags. The bagged material is then inserted and sealed into a high density polyethylene (HDPE) drum or equivalent secondary container. Specifications for the packaging material are presented and the LDPE bag is stated to be suitable for pharmaceutical or "in contact with food" use. A statement for compliance with Commission Regulation (EU) No 10/2011 is provided.

Finished product

The tablets are packaged in PCTFE/PVC/aluminium blister packs with aluminium foil with a heat sealing coating lacquer as backing foil. Specifications for the packaging material components are provided and are satisfactory. A statement of compliance with Commission Regulation (EU) No 10/2011 is provided.

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

The only material of animal origin used in the product or in the production of the active substance is lactose monohydrate. Confirmation is provided that this is manufactured from bovine milk sourced from healthy animals in the same conditions as milk collected for human consumption.

Therefore none of the starting materials used for the active substance or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3).

The CVMP concluded that the risk of transmitting spongiform encephalopathies through APOQUEL has been assessed in compliance with the current regulatory texts and can be considered as negligible.

Control tests during production

Not applicable.

Control tests on the finished product

The specifications proposed at release and at the end of shelf-life are appropriate to control the quality of the finished product. Active substance limits are controlled in accordance with Annex I to Directive 2001/82/EC. Limits for specified, unspecified and total impurities are included on the specifications and are in accordance with the VICH thresholds specified in VICH guideline GL11 on impurities in new veterinary medicinal products (CVMP/VICH/838/99-Rev.1). Other criteria and limits are set in accordance with VICH guideline GL39 on test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: chemical substances (CVMP/VICH/810/04).

Analytical methods and their validation are described for analysis of the assay, purity, content uniformity and dissolution. Other test methods are standard pharmacopoeial methods. The methods are appropriately validated in accordance with VICH guideline GL2 on validation of analytical procedures: Methodology (CVMP/VICH/591/98). Batch data are presented for 7 batches of finished product manufactured using the defined crystalline form of the active substance. The batch data demonstrate full compliance with the specification. Additional supporting data are also provided for batches manufactured using another crystalline form of the active substance.

Stability

Dosage form stability studies have been conducted in accordance with the current version of guideline CVMP/VICH/899/99-Rev.1. Samples of each tablet strength have been stored in the packaging proposed for marketing. Samples were stored at 25 °C/60% RH, 30 °C/65% RH and 40 °C/75% RH. Real time testing was conducted at 30 °C/65% RH. Nine and twelve month data is currently available. Data at 24 months 30 ºC/65% RH is also provided for two supporting batches. Results of the tests demonstrate the product to be stable with no adverse trends in any of the parameters investigated, except a slight decrease in assay under accelerated conditions. Supporting stability results are also provided for batches of finished product manufactured using a different crystalline form and containing a different quantity of magnesium stearate. Based on the data currently available for representative dosage form batches, a maximum shelf life of 24 months when stored below 25 °C is considered acceptable. A photostability study demonstrates the product to be stable on exposure to light and an in-use study for half tablets supports the proposed in-use period of 3 days.

Conclusion on stability

Shelf life of the veterinary medicinal product as packaged for sale: 24 months

Shelf life of unused half tablets: 3 days

Storage conditions: Store below 25 °C.

Overall conclusions on quality

The formulation is typical for an immediate release film-coated tablet. It is manufactured by direct compression using pharmacopoeial grade excipients that are widely used in tablet formulations. Extensive formulation development is described in the dossier, from active substance properties to excipient selection/optimisation and manufacturing process optimisation. The manufacturing process is a standard one using conventional manufacturing techniques. The manufacturing process description is adequately described and includes appropriate in-process controls.

The manufacturing process for the active substance is a chemical synthesis followed by formation of the maleate salt. Details of the process and its control are adequately described in the dossier. One impurity in the active substance is qualified above the VICH qualification threshold specified in VICH guideline GL10 on impurities in new veterinary drug substances (CVMP/VICH/837/99-Rev.1). A limit for this impurity based on the toxicological data provided and the manufacturing capability of the process has been justified.

The specifications proposed at release and at the end of shelf-life are appropriate to control the quality of the finished product. Analytical methods are appropriately validated.

Dosage form stability demonstrates the product to be stable with no adverse trends in any of the parameters investigated, except a slight decrease in assay under accelerated conditions. There is sufficient stability data available to support the proposed shelf life of 2 years when stored below 25 °C. The proposed 3 day in-use shelf life for half tablets when returned to the open blister is supported by the data provided.

Part 3 – Safety

APOQUEL tablets are intended for the treatment of pruritus associated with allergic dermatitis in dogs and for the treatment of clinical manifestations of atopic dermatitis in dogs.

The product is indicated for dogs for the treatment of pruritus associated with allergic dermatitis, and for the treatment of clinical manifestations of atopic dermatitis. For both indications the proposed initial dose is 0.4 mg to 0.6 mg oclacitinib/kg bodyweight administered twice daily for up to 14 days, and after that, for maintenance therapy the same dose is administered only once daily.

APOQUEL tablets contain oclacitinib as active substance. Oclacitinib inhibits the function of a variety of cytokines dependent on Janus kinase (JAK) enzyme activity (a JAK inhibitor). Numerous cytokines are known to activate the JAK family of enzymes when bound to their receptors. These cytokines include pro-inflammatory cytokines as well as cytokines implicated in allergic responses.

The excipients used in the APOQUEL tablet formulation are widely used in approved veterinary and human marketed pharmaceutical products and none are anticipated to be a human user safety concern.

As the excipients of APOQUEL tablets are of limited toxicological potential, the substance of interest regarding user safety is the active ingredient, oclacitinib.

Safety documentation

Pharmacodynamics

See Part 4.

Pharmacokinetics

The pharmacokinetics of oclacitinib in the target species was evaluated in a series of studies conducted in laboratory dogs (beagles and mixed breeds), briefly summarised as follows:

- In dogs, oclacitinib is rapidly and well absorbed following oral administration, with time to peak plasma concentrations (t_{max}) less than 1 hour. Following administration of the final formulation tablet to fasted dogs the absolute bioavailability of oclacitinib was 89%. Following

intravenous administration to laboratory dogs, the total body plasma clearance of oclacitinib was found to be low 316 ml/h/kg bodyweight (5.3 ml/min/kg bw), and the apparent volume of distribution at steady-state was 942 ml/kg bw. The terminal $t_{1/2}$ following intravenous (IV) and oral (PO) administration was similar with values of 3.5 and 4.1 hours, respectively.

- The prandial state of dogs did not significantly affect the rate or extent of absorption of oclacitinib. Additionally, the pharmacokinetics of oclacitinib in laboratory populations of beagles and mixed breed dogs did not appear to be significantly different. Generally, across all the pharmacokinetic studies, there were no significant differences in oclacitinib pharmacokinetics attributable to sex.
- Dose proportionality from 0.6 to 3.0 mg/kg bw was claimed to be confirmed in the pivotal target animal safety study following the first dose, although it appears that some accumulation occurs at higher doses (1.8 and 3 mg/kg bw). The pharmacokinetics of oclacitinib following multiple dosing was also evaluated in the target animal safety study. During the twice daily dosing phase of the study the oclacitinib exposure increased from day 0 to day 21. Following the change in dosing regimen from twice daily to once daily dosing there was a numerical decrease in the oclacitinib plasma exposure over the 24 hour period compared with twice daily dosing. Additionally, it appears that steady-state plasma levels are achieved within a week of the regimen change.
- The oclacitinib protein binding was low with 66.3 - 69.7% bound in fortified canine plasma at nominal concentrations ranging from 10 - 1000 ng/ml.
- Inhibition of canine cytochrome P450 enzymes by oclacitinib is minimal with IC_{50} values at least 50 fold greater than the observed C_{max} values at the proposed use dose. Therefore, the risk of metabolic drug-drug interactions due to oclacitinib inhibition is considered low.

The disposition of oclacitinib was assessed in studies using ^{14}C-oclacitinib. Radioactivity was widely distributed to the tissues up to 24 h post dose. The highest concentrations of total radioactivity were measured in the liver and along the gastrointestinal tract up to 72 h post dose. The main route of excretion of total radioactivity at 72 h post dose was via the urine (approximately 51% of the administered dose), with a significant amount also excreted via the faeces (approximately 38% of the administered dose). Biliary elimination is also a factor in the excretion of ^{14}C-oclacitinib based on the recovery radioactivity in the faeces, bile, and liver. In plasma, parent oclacitinib accounted for 85% and 64% of the total chromatographic radioactivity at 1 and 6 hours post dose, respectively. Parent oclacitinib accounted for a small percentage of the residues in the urine approximately with 3.6% of residues in the 0 to 24 hour sample. Oclacitinib was metabolized in dog, with one major oxidative metabolite identified in plasma and urine. In rats and rabbits, the oral pharmacokinetics was evaluated as part of the toxicology studies. In these studies the exposure (AUC and C_{max}) of oclacitinib increased with increasing dose. The plasma pharmacokinetics on the first day of dosing and those at the end of study (Day 7, 12, 28 or 87) appeared to be similar, indicating no accumulation or induction.

In conclusion, oclacitinib is rapidly and well absorbed following oral administration. The terminal $t_{1/2}$ following oral administration was 4.1 hours. The rate or extent of absorption of oclacitinib did not appear to be influenced by breed, gender or prandial state. Steady-state plasma levels are generally achieved within a week of dosing. The disposition of oclacitinib was assessed in studies using ^{14}C-oclacitinib. Radioactivity was widely distributed to the tissues up to 24 hours post dose. The main route of excretion of total radioactivity was via the urine, with a significant amount also excreted via the faeces). Parent oclacitinib accounted for a small percentage of the residues in the urine. Overall, the major clearance mechanism is metabolism with contributions from renal and

biliary mechanisms. The totality of data presented is considered adequate to characterise the pharmacokinetics of oclacitinib in the target species.

Toxicological studies

The safety of oclacitinib was evaluated in a comprehensive battery of toxicology studies including 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 target animal safety studies in dogs, developmental toxicity studies in rats and rabbits, studies to evaluate genotoxic potential, and local effect studies (acute oral and dermal toxicity studies in rats, ocular and dermal irritation studies in rabbits, and a mouse local lymph node assay). All pivotal studies were conducted in accordance with GLP and relevant OECD guidelines. In summary:

Acute toxicity: In rats, the acute oral maximum asymptomatic dose of oclacitinib was 175 mg/kg bw. The acute oral LD_{50} was estimated to be 310 mg/kg bw. The acute dermal toxicity of oclacitinib in rats was low with a dermal LD_{50} greater than 2000 mg/kg bw.

Repeat-dose toxicity: The repeat-dose studies in rats and dogs were conducted using the oral route of administration. The most sensitive repeat-dose toxicity study was determined to be the 90-day oral dog study where the lowest observed adverse effect level (LOAEL) was oclacitinib 0.25 mg/kg bw/dose (0.5 mg/kg bw/day) based on hypocellularity of lymphoid and hematopoietic tissues. A NOEL could not be determined for any of the studies conducted.

Reproductive toxicity: No studies conducted.

Developmental toxicity: Oclacitinib was not embryo-lethal 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.

Genotoxicity: Oclacitinib is not considered to be of mutagenic or genotoxic concern given the negative findings in a standard battery of tests required by VICH guideline GL23 (EMEA/CVMP/VICH/526/00): two *in vitro* (a test for gene mutation in bacteria and a test for chromosomal effects in mammalian cells) and one *in vivo* (micronucleus assay).

Carcinogenicity: Carcinogenicity studies were not conducted. 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 were no structural alerts for carcinogenicity.

Local effects: Oclacitinib is corrosive (irritation not reversible in 21 days) to rabbit eyes, is a mild/slight irritant to intact rabbit skin, but does not have sensitisation potential.

User safety

The applicant has presented a user safety risk assessment which has been conducted in accordance with CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1), assessing the risks to an adult user handling the tablets and the risk for a child inadvertently swallowing tablets.

The adult user could potentially be exposed to trace amounts of oclacitinib through dermal exposure from handling the tablets, inhalation exposure through breaking of tablets, and ocular and oral exposure from hand-to-eye or hand-to-mouth transfer, respectively. Based on the directions to the user to wash hands after administering APOQUEL tablets to the dog, and film

coating of the tablets, these exposure risks are considered minimal. There has been no consideration of the potential for repeated user exposure although this product is intended for long-term treatment. However, given the nature of the formulation (film-coated tablet), it is accepted that the potential for repeated exposure is likely to be limited.

A toddler accidentally consuming the largest number of tablets for a 55-60 kg dog (two 16 mg tablets) could result in an oral exposure of 32 mg or 3.2 mg/kg bw for a 10 kg child. This dose is 54 times lower than the acute oral maximum asymptomatic dose of 175 mg/kg bw; however, it is acknowledged that when applying a safety factor of 100 there is no margin of safety. As oral exposure in a toddler would be a rare, single event, comparison to the acute single-dose oral exposure study is relevant.

The user safety statements included in the SPC and product labelling will mitigate the low risk to the user from accidental dermal, ocular, or oral exposure and are considered appropriate. The product will be supplied in robust packaging (blister packs) reducing the likelihood of inadvertent exposure of children. In addition, the product labelling will carry the standard warnings "For animal treatment only" and "Keep out of sight and reach of children".

It is concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Environmental risk assessment

A Phase I assessment of environmental exposure based on the characteristics and use pattern of the product was submitted. The product is indicated for use only in non-food animals. As such, a Phase II environmental risk assessment is not required and it can be concluded that the product is not expected to pose a risk to the environment when used as recommended.

Overall conclusions on the safety documentation

Oclacitinib is of moderate hazard following acute oral exposure. Repeat dose studies in rats and dogs resulted in oclacitinib 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 dog study where the lowest observed adverse effect level (LOAEL) was oclacitinib 0.25 mg/kg bw/dose (0.5 mg/kg bw/day) based on hypocellularity of lymphoid and hematopoietic tissues. Oclacitinib was not embryolethal in rats at oral doses $\leq$ 5 mg/kg bw/day or in rabbits at doses $\leq$ 30 mg/kg bw/day and was not teratogenic in rats at oral doses $\leq$ 25 mg/kg bw/day or in rabbits at doses $\leq$ 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 were 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.

The user safety statements included in the SPC and product labelling will mitigate the minimal risk to the user from accidental dermal, ocular, or oral exposure and are considered appropriate. The product will be supplied in robust packaging (blister packs) reducing the likelihood of inadvertent child exposure.

The product is not expected to pose a risk to the environment when used as recommended.

Residues documentation

As the product is only intended for administration to non-food producing species, there are no requirements for residues data.

Part 4 – Efficacy

APOQUEL tablets are intended for the treatment of pruritus associated with allergic dermatitis in dogs and for the treatment of clinical manifestations of atopic dermatitis in dogs. For both indications the proposed initial dose is 0.4 mg to 0.6 mg oclacitinib/kg bodyweight administered twice daily for up to 14 days, and after that, for maintenance therapy the same dose is administered only once daily.

Pharmacodynamics

APOQUEL tablets contain oclacitinib as the active substance. Oclacitinib is a JAK inhibitor. JAK 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 when bound to their receptors. These cytokines include pro-inflammatory cytokines as well as cytokines implicated in allergic responses.

The applicant has investigated the inhibitory effects of oclacitinib on JAK enzyme activity and on JAK dependent cytokines. 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,
- 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.

While some of these cytokines are proinflammatory or implicated in allergic responses/pruritus, these and others exert a wide range of responses in a variety of cell types. For example, a number of JAK-dependent cytokines are important components of host defence or have a role in normal haematopoiesis. Therefore, while JAK inhibitors may have utility in diseases such as atopic dermatitis that involve the dysregulation of cytokine signalling, it would appear that there is potential for a range of other non-target effects (e.g. unwanted effects on host defences, haematopoiesis, etc).

The data presented by the applicant appears to indicate that oclacitinib does not significantly inhibit the function of cytokines such as erythropoietin (EPO) or granulocyte-macrophage colony-stimulating factor (GM-CSF) that are dependent on JAK2 enzyme activity. However, from the safety and efficacy studies, it is evident that there are oclacitinib-related effects on red blood cell and white blood cell parameters. Furthermore, it is noted that in the isolated enzyme assays presented, inhibition of human recombinant JAK1 enzyme and JAK2 enzyme was comparable (IC50 of 10 nM and 18 nM, respectively).

In exploratory *in vivo* studies conducted using a canine flea allergic dermatitis model, oclacitinib produced reproducible anti-pruritic effects at dosages as low as 0.25 mg/kg bw given twice a day.

The onset of anti-pruritic activity was rapid (within 1.5 h) after a single dose of oclacitinib administered at 0.4 mg/kg bw dose. Doses of 0.4 mg/kg bw twice a day or higher also significantly improved skin lesions and erythema within 7 days.

Based on the exploratory studies, two laboratory flea allergic dermatitis model studies were conducted for the purpose of investigating the efficacy of oclacitinib to control flea associated pruritus and skin lesions in dogs when administered at a nominal dosage of 0.4 mg/kg bw. Both studies were conducted in accordance with GCP. The second of these studies provides convincing evidence that oclacitinib administration for up to 14 days results in a significant reduction in pruritus and erythema/lesion scores relative to placebo. In this study, there was no significant improvement in these parameters for the higher dose (0.8 mg/kg bw given twice daily) compared to the intended initial treatment dose (0.4 mg/kg bw twice daily).

To confirm that dogs with naturally occurring atopic dermatitis would respond similarly to dogs with flea allergic dermatitis, the efficacy of oclacitinib (0.4 mg/kg bw twice daily) compared to placebo was evaluated in client-owned dogs. Again, in this study, administration of the test product resulted in a significant reduction in pruritus score and erythema/lesion score relative to placebo.

Based on the data presented above, a nominal dosage of 0.4 mg/kg bw oclacitinib administered orally twice daily was selected for development.

Development of resistance

Not applicable.

Pharmacokinetics

Oclacitinib is rapidly and well absorbed in dogs following oral administration. The terminal $t_{1/2}$ following oral administration was 4.1 hours. The rate or extent of absorption of oclacitinib did not appear to be influenced by breed, gender or prandial state. Steady-state plasma levels are generally achieved within a week of dosing. The disposition of oclacitinib was assessed in studies using ^{14}C-oclacitinib. Radioactivity was widely distributed to the tissues up to 24 hours post dose. The main route of excretion of total radioactivity was via the urine, with a significant amount also excreted via the faeces. Parent oclacitinib accounted for a small percentage of the residues in the urine. Overall, the major clearance mechanism is metabolism with contributions from renal and biliary mechanisms. The totality of data presented is considered adequate to characterise the pharmacokinetics of oclacitinib in the target species.

See Part 3 for more detail.

Dose determination/justification

See section on pharmacodynamics above.

Target animal tolerance

The target animal safety (TAS) studies were conducted over several years. A total of 131 dogs were exposed to oclacitinib doses ranging from 0.5 mg/kg bw (0.25 mg/kg bw twice daily) to 18 mg/kg bw/day (9 mg/kg bw twice daily), and for durations from 10 days to 6 months.

The first 3 studies were conducted in the discovery phase, and included a 10-day tolerance study, a 28-day margin of safety (MOS) study and a 90-day MOS study. These studies were not conducted under GLP compliance and used development formulations containing oclacitinib but with different salts and various excipients. The 90-day study used the maleate salt, which was chosen for the final pharmaceutical development. All discovery studies incorporated twice per day dosing in a population of adult beagle dogs.

Following the completion of the discovery development phase a margin of safety (MOS) study to support chronic twice daily oral dosing was conducted. This GLP study was conducted in young adult beagle dogs, approximately 6 months old at initiation, and used a development formulation. Oclacitinib was administered to dogs at 0, 1, 3, and 5 times the maximum exposure dose of 0.6 mg/kg twice per day. The intended duration of the study was 26 weeks. After 4 months of treatment, two dogs required euthanasia and several dogs in the mid and high dose groups developed clinical demodicosis which was attributed to treatment-related immunosuppression. The study was prematurely terminated at 16 weeks.

The main conclusion from this study was that there was an insufficient MOS to support chronic twice daily dosing. Consequently, three alternative dosing regimens were investigated in a negative controlled US field dose selection study. The results from this dose selection study were in favour of the *jump start* dosing regimen, i.e., 0.4 mg/kg bw twice daily for 14 days, followed by 0.4 mg/kg bw given once a day. The results from the dose selection study were further investigated in a negative controlled field dose confirmation study conducted in the US to evaluate the safety and efficacy of oclacitinib compared to placebo for the control of atopic dermatitis in client-owned dogs. See section on field studies.

Once the final dose regimen was confirmed, the pivotal 6 month, GLP MOS study was conducted. In this study, the product was administered orally, twice per day for 6 weeks, followed by once per day for 20 weeks, to dogs at 1, 3, and 5 times the maximum exposure dose of 0.6 mg/kg (recommended clinical dose is 0.4 mg/kg bw) for a total of 26 weeks (6 months). Because the recommended dose will have an initial 14 day twice daily dosing regimen, the first 6 weeks (3X duration) of this study had twice daily dosing.

The product was generally well tolerated at all doses. However, there were test article effects in all groups consistent with the pharmacological action of the drug class. These included: papillomas (considered test article related, but not dose related); interdigital cysts (pododermatitis, etc) (probably dose-related); decreases in red cell mass; decreases in serum albumin; decreased cellularity of gut-associated lymphoid tissue (GALT), spleen, and cervical/mesenteric lymph nodes; decreased cellularity of sternal and femoral bone marrow. Most of these effects were mild and appeared non-progressive.

The suspected adverse reactions and outcomes observed in the above TAS studies are summarised in the following.

- Generally, the product was well tolerated at the recommended treatment dose with few clinically evident adverse effects, which were typically mild. Skin and appendages disorders (interdigital furunculosis) provided the greatest number of observations in the pivotal 6 month MOS study: the lesions were increased in number and were observed for longer periods of time (as evidenced by the number of observations) as doses increased. Papillomas were occasionally observed in all oclacitinib dose groups over the six months of the study. Gastrointestinal signs, especially diarrhoea and soft stools, were frequently observed in two high dose studies. However, in one of these studies, most cases of early soft stool and diarrhoea were attributed to coccidia and giardia infections. The extent to which

gastrointestinal infection is due to the immunomodulating effect of oclacitinib treatment is unclear,

- In all TAS studies, a total of four dogs were euthanized. These dogs were considered to have succumbed to infection as a result of treatment-related immunosuppression. All of these dogs were on oclacitinib for more than 74 days at doses of ≥ 6X the maintenance dose.
- The most severe adverse clinical effects were observed in dogs aged less than one year. Some of the effects observed in young dogs (relative to adult animals) may be due to differences in immune system competence. As a result of the effects seen in young dogs, the decision was made to limit its use to dogs of greater than 1 year of age.
- Haematological changes were noted in studies at almost all doses and durations; however, they were generally mild and recovered after treatment was stopped. Changes in white cell parameters from the various studies were less consistent. The oclacitinib-related effect on the erythroid line of cells is indicative of some amount of JAK2 inhibition activity.
- In a number of studies there was evidence of decreased cellularity (lymphoid) of gut associated lymphoid tissue (GALT), spleen, and cervical/mesenteric lymph nodes; decreased cellularity of sternal and femoral bone marrow. These effects may impact the ability of the immune system to adequately fight off challenge with bacterial, parasitic, or viral infections. However, at the recommended treatment dose these effects were mild and appeared non-progressive. Again, these findings were attributed to the pharmacological activity of the test article.
- On clinical chemistry, the most consistent finding was a reduction in blood protein (albumin and/or globulin).

The safety of oclacitinib was investigated at multiples of the recommended treatment dose (RTD) for up to six months. Notwithstanding the fact that this product will be administered to atopic dogs long-term, the Committee agreed that more long-term laboratory safety studies are unlikely to yield more information than that already learned from the available 6 month studies given that accumulation of oclacitinib is not expected and that the clinicopathological and histopathological effects noted at six months are comparable to those noted at 3 months, indicating limited evidence of progression. Therefore the absence of more long-term laboratory safety studies in the target animal is accepted.

Finally, a GLP study was conducted to evaluate the ability of the young dog (n=16, age 16 weeks) to respond serologically to primary vaccination while receiving oclacitinib at 3 times the twice daily dose. The Committee concluded that the data presented appear to indicate an effect of treatment on immunological response to vaccination with canine parainfluenza virus (CPI) and rabies virus (RV). For these two antigens, the antibody titres post-vaccination in oclacitinib-treated pups were smaller than those achieved in controls. The clinical relevance of this effect remains unclear. A statement to this effect is included in section 4.8 of the SPC.

Field trials

APOQUEL is intended for use for:

1. Treatment of pruritus associated with allergic dermatitis in dogs ("pruritus claim").

   The SPC includes a special precaution (section 4.5) that the underlying cause of the pruritis should be investigated and the appropriate treatment initiated.

2. Treatment of clinical manifestations of atopic dermatitis in dogs ("atopic dermatitis" claim).

For both indications the proposed dose of APOQUEL (oclacitinib maleate) is 0.4 mg/kg bodyweight, up to a maximum of 0.6 mg/kg bodyweight, administered twice daily for up to 14 days, and then administered once daily for maintenance therapy.

The applicant conducted a total of 4 pivotal field studies – one in the EU and three in the US - and two supportive studies to support the two different clinical indications and to provide information on clinical safety. There are a number of features common to various clinical efficacy studies presented. These are:

- All field studies presented were conducted in accordance with GCP.
- The studies were performed with the final product formulation (intended commercial product), i.e. oclacitinib tablets for oral administration with three different strengths (3.6 mg, 5.4 mg and 16 mg).
- The inclusion criterion for the studies to support the pruritus claim was "moderate" pruritus as a minimum (documented by owners), with or without dermatitis.
- All dogs enrolled in the Atopic Dermatitis studies were required to have a documented history of chronic, non-seasonal Atopic Dermatitis (disease present or recurrent). Since atopic dermatitis does not have definitive diagnostic criteria, establishment of the diagnosis was made upon compatible history and clinical signs, and exclusion of other diagnoses.
- In all efficacy studies, a primary variable for treatment success based on assessment of pruritus by the owner is included as a primary efficacy variable. The degree of pruritus of the dog over the previous 24 hours was assessed subjectively by the owner through the use of an enhanced visual analogue scale (VAS). This scale combines behavioural features and severity based information with the visual analogue scale.
- In the four atopic dermatitis studies, in addition to assessment of pruritus by the owner, the other primary efficacy variable is based on investigator assessment of skin lesions using the Canine Atopic Dermatitis Extent and Severity Index (CADESI). In the two pivotal and one supportive US atopic dermatitis studies, CADESI-02 was used to quantitatively describe the skin condition by assessing three skin variables, erythema, lichenification and/or excoriation in each of 40 different body regions as "Normal or absent" (0), "Mild" (1), "Moderate" (2), or "Severe" (3). In the EU study, CADESI-03 was employed. CADESI-03 is different from CADESI-02 in that it has an increased number of body sites (62 *vs.* 40), it adds another clinical sign (self-induced alopecia) and in its ability to grade each sign in a wider scale (from 0 to 5, compared to 0 to 3).

The pruritus claim was investigated in two pivotal field studies - one in the EU [n=220] and one in the US [n=436] - to treat pruritus associated with allergic dermatitis. The EU study included an active control, prednisolone, while oclacitinib was compared to placebo in the US study. In the US study superiority versus placebo was demonstrated (success rates of 67% and 29% for the oclacitinib and placebo groups, respectively). In the EU study, the treatment success rate was 68% for the oclacitinib treated group compared to 76% for prednisolone-treated dogs. Although non-inferiority to prednisolone was not confirmed in the EU study, it is clear that oclacitinib had a marked anti-pruritic effect relative to pre-treatment pruritus score.

Based upon both studies, it can be concluded that efficacy for the treatment of pruritus has been demonstrated at a dose regimen of 0.4 mg/kg bodyweight, up to a maximum of 0.6 mg/kg bodyweight, administered twice daily.

For the atopic dermatitis indication, the applicant submitted two placebo-controlled field efficacy studies conducted in the US as pivotal evidence to support the claim "Treatment of clinical manifestations of atopic dermatitis in dogs" when APOQUEL is administered in accordance with the proposed dose regimen. One study was designed as a dose determination study [n=220], the other as a dose confirmation study [n=299]. In the pivotal dose confirmation study, the treatment success for oclacitinib (per protocol analysed after 28 days of treatment) was 66% for the pruritus scores (4% in placebo-treated animals) and 49% for CADESI scores (4% in placebo-treated animals). Both success rates were highly statistically different ($p<0.0001$) compared to placebo. A similar success rate was achieved in the dose determination study. It can be concluded that oclacitinib is effective in the treatment of clinical manifestations of atopic dermatitis.

In addition, two field studies - one conducted in the EU [n=269] and one conducted in the US [n=342] - in which the continuous twice daily dosing regimen of 0.4 mg/kg bw was investigated are submitted as supportive evidence. This non-pivotal EU study was designed as a controlled study, using cyclosporine as the positive control. In this study, oclacitinib was non-inferior to cyclosporine treatment. However, it should be noted that dogs received oclacitinib twice daily continuously in this study, instead of once daily from day 14 onwards.

In conclusion, efficacy was demonstrated for the atopic dermatitis indication at the proposed dose regimen 0.4 mg/kg bodyweight, up to a maximum of 0.6 mg/kg bodyweight, administered twice daily for up to 14 days, and then administered once daily for maintenance therapy (up to 112 days).

Overall, based upon two GCP-compliant field studies investigating the efficacy of the product for the treatment of pruritus associated with allergic dermatitis in dogs with at least moderate pruritus, it can be concluded that efficacy for the treatment of pruritus has been demonstrated at doses 0.4 mg/kg bodyweight, up to a maximum of 0.6 mg/kg bodyweight, administered twice daily for up to 14 days.

Based upon two GCP-compliant field studies investigating the efficacy of the product for the treatment of treatment of clinical manifestations of atopic dermatitis in dogs, it is concluded that efficacy for the treatment of atopic dermatitis has been demonstrated at doses 0.4 mg/kg bodyweight, up to a maximum of 0.6 mg/kg bodyweight, administered twice daily for up to 14 days, and then administered up to 112 days once daily for maintenance therapy.

The effectiveness of maintenance therapy (once daily treatment, from day 14 onwards) has been demonstrated for the control of pruritus in atopic dermatitis dogs, but has not been tested for the control of pruritus in other allergic dermatitis conditions like contact dermatitis, flea allergic dermatitis and food allergy. Based on the mode of action, it is reasonable to assume that the maintenance therapy in these animals will be as effective as it was in the atopic dermatitis animals. Therefore, the extension of the duration of maintenance therapy to the pruritus claim is justified. Due to the potential for adverse effects, it is considered appropriate that the SPC include advice that the requirement for long-term maintenance therapy should be based on an individual benefit-risk assessment.

In general terms concerning clinical safety, APOQUEL was observed to be well tolerated when administered for up to 112 days. In the four pivotal field studies, diarrhoea, emesis, anorexia, dermatitis, pyoderma and otitis externa were the most frequently reported abnormal clinical signs in the oclacitinib treatment groups. However, the majority of the safety information was generated in a single arm phase of these studies (that is, no placebo control); therefore, it is not possible to be clear on causality. In particular, the extent to which infections such as pyoderma, dermatomycoses, otitis and dermatitis are due to the immunomodulating effects of the treatment

is unclear. It is possible that these conditions are due in part to alternation in skin barrier function caused by the underlying disease process.

A comprehensive review of haematology, chemistry and urinanalysis results with mean values for individual analytes remaining within the normal reference ranges suggests that oclacitinib exerts no long-term effects on any analyte or group of analytes. Oclacitinib-treated dogs appeared to respond appropriately to the concurrent administration of a wide variety of other medications and therapies.

In the various field studies, there are a number of reports of neoplasia developing/becoming clinically evident after weeks of treatment. Notwithstanding the arguments presented in the dossier that there would be no increase in malignancy rate over time and that the types of tumours/incidence rates in the field studies is in line with what is expected in the general dog population, the CVMP remains concerned, given the immunomodulating effect of this product and the likely use in an individual patient for prolonged periods of time (potentially long-term) that treated dogs may be more susceptible to neoplasia. CVMP considers that in the absence of a time-matched placebo control group, it is not possible to definitively exclude an effect of treatment on the development of neoplasia in the field studies. In view of this concern, the following text was included in the SPC: "Oclacitinib modulates the immune system. Oclacitinib may increase susceptibility to infection and may exacerbate neoplastic conditions. Dogs receiving oclacitinib should be monitored for the development of infections and neoplasia".

In conclusion, while APOQUEL was observed to be generally well tolerated when administered at the recommended treatment dose for up to 112 days, adverse effects such as diarrhoea, emesis, anorexia, dermatitis, pyoderma and otitis externa were reported. Tolerance in the field after long-term (>112 days) treatment has not been comprehensively investigated. Given the immunomodulating effect of this product and the likely long-term use in an individual patient, it is considered that oclacitinib may increase susceptibility to infection and may exacerbate neoplastic conditions.

Overall conclusion on efficacy

Four pivotal field studies (one in the EU and three in the US) were submitted to demonstrate the efficacy of the product for two different clinical indications. In addition two supportive field studies – one conducted in the US and one in EU - were submitted concerning the atopic dermatitis indication.

Overall, based upon two GCP-compliant field studies investigating the efficacy of the product for the treatment of pruritus associated with allergic dermatitis in animals with at least moderate pruritus, it can be concluded that efficacy for the treatment of pruritus has been demonstrated at doses 0.4 mg/kg bodyweight, up to a maximum of 0.6 mg/kg bodyweight, administered twice daily for up to 14 days.

Based upon two GCP-compliant field studies investigating the efficacy of the product for the treatment of treatment of clinical manifestations of atopic dermatitis in dogs, it is concluded that efficacy for the treatment of atopic dermatitis has been demonstrated at doses 0.4 mg/kg bodyweight, up to a maximum of 0.6 mg/kg bodyweight, administered twice daily for up to 14 days, and then administered up to 112 days once daily for maintenance therapy.

The maintenance therapy of once daily dosing beyond 14 days has been confirmed for the atopic dermatitis indication and it is justified to apply this to the pruritus indication, however, given the

safety concerns related to long-term treatment, it is recommended that long-term maintenance therapy should be based on an individual benefit-risk assessment,

Concerning clinical safety while APOQUEL was observed to be generally well tolerated when administered at the recommended treatment dose for up to 112 days, adverse effects such as diarrhoea, emesis, anorexia, dermatitis, pyoderma and otitis externa were reported. These potential adverse effects are detailed in section 4.6 of the SPC. Tolerance in the field after long-term (>112 days) treatment has not been comprehensively investigated. Given the immunomodulating effect of this product and the likely long-term use in an individual patient, it is considered that oclacitinib may increase susceptibility to infection and may exacerbate neoplastic conditions. A statement to this effect is included in the SPC.

Part 5 – Benefit-risk assessment

Introduction

APOQUEL film-coated tablets contain oclacitinib (as oclacitinib maleate) as the active substance. There are three different strengths of the tablets (3.6 mg, 5.4 mg and 16 mg oclacitinib) and each is contained in blister packs (PCTFE/PVC/aluminium) which are supplied in outer cartons containing 20 or 100 tablets. The route of administration is oral use. The target species is dogs. The product is indicated for the treatment of pruritus associated with allergic dermatitis in dogs and the treatment of clinical manifestations of atopic dermatitis in dogs.

Oclacitinib is a new active substance.

Benefit assessment

Direct therapeutic benefit

In four well-conducted pivotal field studies, efficacy was been confirmed for use of the product in the treatment of pruritus associated with allergic dermatitis in dogs and the treatment of clinical manifestations of atopic dermatitis in dogs. Therefore, animals suffering from clinical manifestations of atopic dermatitis or pruritus associated with allergic dermatitis would benefit from treatment with this product.

Additional benefits

APOQUEL increases the range of available treatment possibilities for the recommended indications.

Risk assessment

Quality: The formulation and manufacture of the product is well described and specifications set will ensure that a product of consistent quality will be produced. One impurity in the active substance is qualified above the VICH threshold specified in VICH guideline GL10 on Impurities in new veterinary drug substances (CVMP/VICH/837/99-Rev.1). The limit applied to this impurity is based on the toxicological data provided and the manufacturing capability of the process and is justified.

Target animal safety: In the laboratory safety studies, the product was generally well tolerated at the recommended treatment dose with few clinically evident adverse effects, which were typically mild. Most observations were for dose-dependent skin and appendages disorders (interdigital

furunculosis) in the pivotal safety study. Papillomas were occasionally observed in all oclacitinib dose groups for the duration of the study. Gastrointestinal signs, especially diarrhoea and soft stools, were frequently observed in two high dose studies. In the field studies, APOQUEL was observed to be generally well tolerated when administered at the recommended treatment dose for up to 112 days. Adverse reactions such as diarrhoea, emesis, anorexia, dermatitis, pyoderma and otitis externa were reported. Adverse effects detected in the target animal safety/field studies and attributed to oclacitinib are detailed in the SPC. Tolerance in the field after long-term (>112 days) treatment has not been comprehensively investigated. Therefore, the implications of long-term use on the ability to fight infection and tumour development are, as yet, unclear. These concerns cannot be evaluated further within the context of the present application and the safety profile can only be further characterised in post-authorisation safety surveillance.

It is not expected that the product will present a risk to the user or the environment when used in accordance with the SPC recommendations.

Risk management or mitigation measures

The proposed risk management measures regarding the user are considered appropriate.

Regarding safety in the target species, adverse effects detected in the target animal safety/field studies and attributed to oclacitinib are detailed in the SPC.

It is considered that the concerns in respect of the potential for increased risk of infections/neoplasia are addressed to some extent by the warning statements included in the SPC:

"Oclacitinib modulates the immune system. Oclacitinib may increase susceptibility to infection and may exacerbate neoplastic conditions. Dogs receiving oclacitinib should be monitored for the development of infections and neoplasia."

By providing this information to veterinary practitioners, this potential risk can be taken into account when considering the choice of treatment.

As advised above, it is considered that the safety profile of this product can only be further characterised following introduction of the product to the field (that is, based on pharmacovigilance experience post-authorisation).

Evaluation of the benefit-risk balance

The product has been shown to have a positive benefit-risk balance overall.

The product has been shown to be efficacious for treatment of pruritus associated with allergic dermatitis in dogs and treatment of clinical manifestations of atopic dermatitis in dogs.

The formulation and manufacture of APOQUEL is well described and the specifications set will ensure that product of consistent quality will be produced.

Tolerance in the target species has been appropriately investigated and the potential adverse reactions are clearly detailed in the SPC.

APOQUEL presents a low risk for users and the environment and appropriate warnings have been included in the SPC.

Conclusion

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

Based on the original and complementary data presented, it is concluded that the quality, safety and efficacy of APOQUEL were considered to be in accordance with the requirements of Directive 2001/82/EC.