Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Apoquel 3.6 mg Chewable Tablets for Dogs
Apoquel 5.4 mg Chewable Tablets for Dogs
Apoquel 16 mg Chewable Tablets for Dogs

Date Created: January 2022

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Apoquel 3.6 mg Chewable Tablets for Dogs Apoquel 5.4 mg Chewable Tablets for Dogs Apoquel 16 mg Chewable Tablets for Dogs
Applicant	Zoetis UK Limited 1st Floor, Birchwood Building Springfield Drive Leatherhead Surrey KT22 7LP
Active substance	Oclacitinib (as oclacitinib maleate)
ATC Vetcode	QD11AH90.
Target species	Dogs
Indication for use	Treatment of pruritus associated with allergic dermatitis in dogs. Treatment of clinical manifestations of atopic dermatitis in dogs.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	MA Extension application in accordance with Article 12.3 of Directive 2001/82/EC as amended. A line extension to add a palatable tablet range to the existing marketing authorisation of Apoquel 3.6 mg Film-coated Tablet for Dogs, Apoquel 5.4 mg Film-coated Tablet for Dogs and Apoquel 16 mg Film-coated Tablet for Dogs originally authorised via the Centralised procedure in September 2013.
Date of conclusion of the procedure	24/11/2021

I. SCIENTIFIC OVERVIEW

The application is for an MA submitted in accordance with Article 12.3 of Directive 2001/82/EC, as amended by 2004/28/EC; a line extension to add a palatable tablet range to the existing marketing authorisation of Apoquel 3.6 mg Film-coated Tablet for Dogs, Apoquel 5.4 mg Film-coated Tablet for Dogs and Apoquel 16 mg Film-coated Tablet for Dogs authorised via the Centralised procedure in September 2013.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] The product is safe for the user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains oclacitinib as its maleate salt (3.6mg,5.4mg and 16mg) and the excipients pork liver powder, crospovidone (Type A), sodium starch glycolate (Type A), glycerol monostearate 40-55 (Type II)

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

macrogol 3350, glycerol, sodium chloride, xanthan gum, dried brewer's yeast, silica, colloidal anhydrous and magnesium stearate

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 choice of the formulation and the absence of preservative are justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of granulation of the active substance and excipients followed by blending with additional excipients and compression

An appropriate process validation protocol was provided and full scale validation will be performed post-authorisation and prior to commercialization. This is supported by current relevant European guidelines

II.C. Control of Starting Materials

The active substance is oclacitinib maleate an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

The excipients are crospovidone (Type A), sodium starch glycolate (Type A), glycerol monostearate 40-55 (Type II), macrogol 3350, glycerol, sodium chloride, xanthan gum, silica, colloidal anhydrous and magnesium stearate which are controlled in with their respective European Pharmacopoeia monographs. Pork liver powder and dried brewers yeast are controlled with an in-house monograph.

II.C.4. Substances of Biological Origin

The applicant has supplied suitable TSE declarations for the active and excipients; compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.
The only excipient of animal origin is pork liver powder which does not contain TSE risk materials of ruminant origin and is treated to inactivate viruses

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable

II.E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification. Control tests on the finished product are those for appearance, identification, assay, degradation, impurity, uniformity, dissolution, water content and microbial limits.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Store in the original package in order to protect from moisture.

Remaining tablet parts should be stored in the blister and be given at the next administration.

Shelf life of the veterinary medicinal product as packaged for sale in blisters: 2 years.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

No data have been submitted in support of the pharmacological and toxicological sections of the application as the active substance is qualitatively and quantitatively identical to the reference products. This approach was considered acceptable as bioequivalence with the reference product is satisfactorily demonstrated.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users / the environment / consumers. Add any additions made to the SPC for the proposed product.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the applicant has satisfactorily addressed the potential risk to children resulting from accidental oral exposure.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore, the following applicant's user recommendations are appropriate:

Wash hands after administration.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
Ingestion of this product may be harmful for children. To avoid accidental ingestion, administer the tablet(s) to the dog immediately after removal from the blister packaging.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:
The applicant has worked through the VICH Phase 1 decision tree and concluded that the proposed product stops at Question 3 as the product is for use in dogs only.

The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

The applicant stated that the proposed dosage and treatment schedule was justified in detail, in the dossier for the initial marketing authorisation application of Apoquel Film-coated Tablets, which have the same posology. The dose justification consisted of three interdependent elements; dose determination studies employing a laboratory flea allergic dermatitis model; a field dose selection study conducted under field conditions in client-owned dogs diagnosed with atopic dermatitis; and supporting pharmacokinetic/pharmacodynamic relationship considerations.

The candidate formulation contains the same quantity of the active substance, oclacitinib, as the original FCT formulation authorised in the EU in 2013. The applicant stated that as the dosage and treatment schedule will be consistent

between products, a bioequivalence study was conducted to demonstrate bioequivalence between the candidate and reference product. As bioequivalence could be demonstrated for $AUC_{0\text{-}t(last)}$ but for not for C_{max}, the applicant submitted; a PK/PD approach using an established model to demonstrate the insignificance of the lower C_{max} in terms of efficacy and an IL-31 challenge efficacy study which, definitively shows that efficacy is similar for the chewable tablet and film coated tablet near the time of C_{max}.

Tolerance in the Target Species

Tolerance studies were not required because the applicant claimed an exemption from the requirement to perform a margin of safety study for Apoquel Chewable Tablets. It was agreed that the conditions by which a new formulation may be granted an exemption (as laid out in VICH GL43) have been fulfilled: the toxicological and target species safety profile for the active substance have been fully evaluated in the course of the authorisation of Apoquel FCT; the existing product is in widespread clinical use; and the bioequivalence study provided sufficient assurance that the systemic exposure resulting from use of the new formulation is expected to be sufficiently similar to that when using the existing formulation to not raise any new target animal tolerance concerns.

IV.II. Clinical Documentation

Laboratory Trials

Palatability studies
Three studies were conducted with the purpose of assessing the palatability of the new formulation of Apoquel tablets for dogs. All three studies used the final intended formulation.

In the pivotal study, 25 healthy colony dogs were offered the product twice a day on seven consecutive days. The treatments were administered according to the dosing table in the proposed SPC, based on the bodyweight of the dogs. In the acceptance tests, the dogs had two minutes' time to prehend and fully consume the entire dose offered. In total, dogs voluntarily and fully consumed the offered dose on 273 out of 346 occasions. Therefore, the overall voluntary acceptance rate of Apoquel Chewable Tablets for Dogs was 78.9%. While the palatability guideline requires the acceptance rate for dogs to be at least 80% for a palatability claim, the acceptance rate in the pivotal study was only marginally below this threshold.

In order to provide further evidence for the palatability of Apoquel Chewable Tablets for Dogs the applicant submitted the results of two additional palatability studies.

In the field study conducted in the US with 121 client-owned dogs suffering from atopic dermatitis or allergic dermatitis, the voluntary acceptance rate of the product was high at 91.6%. The study was of high quality (GCP-compliant) and

fulfilled most requirements of the CVMP guidelines on the demonstration of palatability, therefore its results are relevant for the current marketing authorisation application.

Further support was provided from a very similar palatability field study) that was conducted with Clavamox Chewable Tablets in dogs using an almost identical protocol as the current field study. In the Clavamox palatability study, the full consumption of the entire offered dose was evaluated at two timepoints, two and five minutes after the dog had access to the tablets. Of the 1567 tests, Clavamox Chewable tablets were fully consumed within two minutes 81.17% of the time and within five minutes 82.51% of all occasions.

For the high acceptance rate of Apoquel Chewable Tablets for Dogs further evidence was provided from the supportive formulation finding study where the product was fully consumed within two minutes in 84.8% of all 283 tests by up to 95 dogs.
Based upon the overall results of the three studies, it was concluded that the data provided supports a palatability claim for Apoquel Chewable Tablets for Dogs.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics the benefit/risk profile of the products is favourable.

MODULE 4

POST- AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

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The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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