Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Zenrelia 4.8 mg Film-coated Tablets for Dogs
Zenrelia 6.4 mg Film-coated Tablets for Dogs
Zenrelia 8.5 mg Film-coated Tablets for Dogs
Zenrelia 15 mg Film-coated Tablets for Dogs

Date Created: August 2025

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Zenrelia 4.8 mg Film-coated Tablets for Dogs, Film-coated tablet Zenrelia 6.4 mg Film-coated Tablets for Dogs, Film-coated tablet Zenrelia 8.5 mg Film-coated Tablets for Dogs, Film-coated tablet Zenrelia 15 mg Film-coated Tablets for Dogs, Film-coated tablet
Applicant	Elanco GmbH, Heinz-Lohmann Strasse 4, Groden, D-27472 Cuxhaven, Germany
Active substance	Ilunocitinib
ATC Vetcode	QD11AH92
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	Full application in accordance with Article 8 of Veterinary Medicine Regulations (VMRs) 2013 (Schedule 1, Part 1) as amended.
Date of conclusion of the procedure	07/08/2025

I. SCIENTIFIC OVERVIEW

The products were submitted for full applications for authorisation in Great Britain (GB), in accordance with Article 8 of Veterinary Medicine Regulations (VMRs) 2013 (Schedule 1, Part 1) as amended.

Zenrelia film-coated tablets contain ilunocitinib at a strength of 4.8, 6.4, 8.5, or 15 mg/tablet. The products are indicated for the treatment of pruritus associated with allergic dermatitis in dogs and the treatment of clinical manifestations of atopic dermatitis in dogs. The recommended dose is 0.6-0.8 mg ilunocitinib/kg bodyweight, administered once daily.

The products are produced and controlled using validated methods and tests which ensure the consistency of the products released on the market. It has been shown that the products can be safely used in the target species and any reactions observed are indicated in the SPC[1]. The products are 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 products 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 ilunocitinib and the excipients microcrystalline 302 cellulose, calcium hydrogen phosphate dihydrate, pregelatinised starch, povidone K30, magnesium stearate and Opadry QX 321 A220011 Yellow.

The container/closure system consists of aluminium/aluminium blisters, with a single film-coated tablet per blister. Each strip contains 10 blisters, and these are

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

packed into an outer cardboard box. The particulars of the containers and controls performed were provided and conform to the regulation.

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 regulatory 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 product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches has been performed post-authorisation.

II.C. Control of Starting Materials

The active substance is ilunocitinib, a novel active substance in GB. 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 microcrystalline cellulose, pregelatinised starch, calcium hydrogen phosphate dihydrate, povidone K30, and magnesium stearate all comply with their corresponding Ph. Eur. (European Pharmacopoeia) monograph. Opadry QX 321A220011 Yellow is compliant with the Commission Regulation (EU) No. 231/2012 for Food Additives and each component of it complies with the relevant Ph. Eur. monograph or Commission Regulation (EU) No. 231/2012.

Data has been supplied to show that the finished product packaging is satisfactory.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the Transmissible Spongiform Encephalopathy (TSE) Guideline present or used in the manufacture of this product.

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 production sites have been provided demonstrating compliance with the specification.

Control tests on the finished product are those appropriate for this type of dosage form.

II.F. Stability

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

G. Other Information

The shelf life of the product as packaged for sale is 2 years. Any remaining half tablets should be stored in the blister and discarded if not used within 20 days.

The product does not require any special storage conditions.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

These are full applications where the applicant supplied bibliographic and trial data to support the product safety. These are summarised in the sections below.

III.A Safety Documentation

Pharmacological Studies

Bibliographical and *in vitro* study data has been provided to illustrate the pharmacodynamics of ilunocitinib. It is a non-selective Janus kinase (JAK) inhibitor and inhibits the function of a variety of pruritogenic and pro-inflammatory cytokines. It also inhibits cytokines involved in allergy which are dependent on JAK enzyme activity. Ilunocitinib has been demonstrated *in vitro* to exert effects on the function of several cytokines involved in haematopoiesis and the innate immune response.

The applicant provided pharmacokinetic data in the target species. Ilunocitinib is rapidly and well absorbed after oral administration in dogs. After oral administration of the tablet at 0.8 mg/kg ilunocitinib in fed dogs, the absolute bioavailability was 80%, and the peak serum concentration (Cmax) was 268 ng/ml. The elimination half-life was 5.0 hours. In fasted dogs, oral bioavailability was 58% showing a similar elimination half-life to fed dogs (5.4 hours) and the Cmax was 122 ng/ml. The time to peak plasma concentrations (Tmax) was between 1 to 4 hours.

After intravenous (IV) administration of 0.8 mg/kg, ilunocitinib had a low plasma clearance of 437 ml/h/kg. The volume of distribution was 1.58 L/kg and terminal half-life was 4.4 hours.

Ilunocitinib exhibits low and consistent protein binding with approximatively 50% bound in fortified dog plasma.

Most of the drug is excreted unchanged in the faeces and urine, with only a small percentage metabolised.

Toxicological Studies

The applicant has conducted laboratory studies which show the following toxicology results:

- Single Dose Toxicity
  - An acute dose toxicity study in rats established an oral LD_{50} (median lethal dose) of >2000 mg/kg.
- Repeated Dose Toxicity
  - A 28-day study in rats established an oral LOAEL (lowest observable adverse event level) of 50 mg/kg/day, in males, and 75 mg/kg/day, in females.
  - A 6-month study in dogs established a NOAEL (no observable adverse event level) of 0.8 mg/kg/day.
- Reproductive Toxicity:
  - A maternal NOAEL of 50 mg/kg/day and a foetal LOAEL of 1 mg/kg/day was determined in rats.
  - Maternal and foetal NOAELs of 10 mg/kg/day were established in rabbits.
  - In dogs, no gross or histopathologic changes in reproductive organs/tissues changes were reported up to the maximum dose tested (4 mg/kg/day).
- Mutagenicity
  - *In vivo* and *in vitro* studies concluded that ilunocitinib is negative for mutagenic potential.
- Carcinogenicity
  - The available supporting data shows ilunocitinib lacks carcinogenic potential.

Studies of Other Effects

The applicant has conducted additional studies which show that the final product formulation is not considered to be an eye or skin irritant and ilunocitinib, does not have the potential to cause skin sensitisation.

Observations in Humans

No human data are available for ilunocitinib as the active ingredient is not used in human medicine.

User Safety

A user risk assessment was provided in compliance with the relevant guideline.

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:

- Accidental ingestion of the product may cause gastro-intestinal effects.
- In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
- Wash hands after administration.

Environmental Safety

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

The applicant provided a Phase I Environmental Impact Assessment (EIA). The product will only be used in non-food producing animals and as a result environmental exposure will be low. A Phase II ERA was not required.

IV. CLINICAL DOCUMENTATION

Due to the legal basis of the applications, the applicant provided trial data to support the clinical efficacy and dosage.

IV.I. Pre-Clinical Studies

Pharmacology

As detailed in section III.A, the applicant has conducted studies and provided data describing the pharmacodynamic and pharmacokinetic properties of the active substance.

Tolerance in the Target Species

In a target species tolerance study, ilunocitinib tablets (final marketed formulation) were administered to 11–12-month-old dogs, once daily for 6 months at 0.8, 1.6, 2.4 and 4.0 mg/kg bw (1, 2, 3 and 5x the recommended treatment dose, respectively). Prior to this, a similar target species tolerance pilot study was carried out with a near-final ilunocitinib tablet formulation. Clinical signs recorded in one or both of these studies that were likely to be related to ilunocitinib treatment included: generalised demodicosis, gum infections, interdigital cysts with or without discharge, papillomas, swollen feet (attributed to interstitial oedema), scabs on the paws and paw thickening and/or discolouration.

A mild-moderate reduction in red blood cell mass was recorded in animals administered 2x to 5x the recommended treatment dose of ilunocitinib. This was of no apparent clinical relevance in any of the treated animals. Additionally, mild and transient decreases in counts of eosinophils were recorded but were not linked to adverse events when the product was administered at 1x the recommended dose.

Emesis and diarrhoea were noted as adverse events in the variety of clinical safety studies performed.

The results have been reflected in appropriate precautions in the SPC.

Studies satisfactorily concluded that there is no potential for long-term accumulation. Therefore, no maximum duration of use is specified.

IV.II. Clinical Documentation

Dose confirmation studies

The applicant conducted five dose determination laboratory studies under controlled conditions using two different, acceptable models of induced pruritus and skin lesions.

The studies were performed in the target species, giving the treatment via the oral administration route. Doses tested were between 0.1 - 2 mg/kg daily.

One GCP-compliant dose determination study was conducted under field conditions. Once daily ilunocitinib was tested at three different dosages (0.25-0.4 mg/kg bw, 0.4-0.6 mg/kg bw and 0.6-0.8 mg/kg bw) compared to placebo.

The conclusions of the dose determination studies adequately support the recommended dose for ilunocitinib of 0.6 – 0.8 mg/kg daily.

Field Trials

To provide the pivotal support for the two clinical indications, the applicant conducted three GCP-compliant, randomised, controlled field trials. These studies were also conducted to support the safety of the product.
To support the first indication of the 'treatment of pruritus associated with allergic dermatitis in dogs', a multi-site field trial was conducted in US veterinary practices. The product was compared to a placebo in a population of 306 client owned dogs with allergic dermatitis. The product was given at the recommended dose, over a time of up to 112 days. The primary efficacy endpoint was pruritus reduction, with treatment success defined as a reduction of 50% or more from baseline score on at least five out of the first seven days of week 1. Results of the study support treatment efficacy and a statistically significant difference in the number of dogs meeting the criteria for success was seen, between dogs treated with the product and placebo. 51.4% of dogs treated with the product had pruritus scores in the normal range by day 28, compared with 15.3% of placebo treated dogs.

To support the second indication of 'treatment of clinical manifestations of atopic dermatitis in dogs', the applicant conducted two further GCP-compliant, randomised, controlled field trials. One of these took place in EU member states and the other was done in North America.

The North American study, conducted in veterinary practices, compared the product with placebo in 268 dogs. The product was given at the recommended dose over a time of up to 112 days. The primary efficacy endpoint was the proportion of dogs achieving treatment success, defined as pruritus reduction or lesion scores reduction of 50% or more at day 28. Results showed that 82.9% of dogs given the product achieved 'treatment success' compared with 30.9% of placebo treated dogs.

The EU trial compared the product with an authorised control product, containing the active ingredient oclacitinib. The products were given to a population of 338 dogs, at the recommended doses, over a time of up to 112 days. For the primary efficacy endpoint, both pruritus reduction and lesion scores reduction were assessed. Results for lesion and pruritus scores showed significant reduction from baseline to day 28, and when the groups were compared, a statistically significant difference was found that was in favour of the ilunocitinib product. The study concluded non-inferiority of the product compared to the control.

In addition to these clinical results, the studies were also supportive of the safety of the product, with the most common signs seen related to digestive tract disorders.

In summary, the clinical trials support the safety and efficacy of the recommended dose of the product for the treatment of pruritus associated with allergic dermatitis in dogs and the treatment of clinical manifestations of atopic dermatitis in 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.

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

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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