Product Name: APOQUEL 3.6 MG TABLETS FOR DOGS
APVMA Approval No: 68311 / 115483

RLP
APPROVED

Label Name:	APOQUEL 3.6 MG TABLETS FOR DOGS

Signal Headings:	PRESCRIPTION ANIMAL REMEDY KEEP OUT OF REACH OF CHILDREN FOR ANIMAL TREATMENT ONLY READ SAFETY DIRECTIONS BEFORE OPENING OR USING

Constituent Statements:	Each tablet contains 3.6 mg oclacitinib maleate

Claims:	For the treatment of pruritus associated with allergic dermatitis in dogs. For the treatment of the clinical manifestations of atopic dermatitis in dogs.

Net Contents:	20 or 100 x 3.6 mg Tablets

Directions for Use:	

Restraints:	

Contraindications:	This product is contraindicated in animals with known hypersensitivity to oclacitinib. This product is contraindicated in dogs with evidence of immune suppression such as hyperadrenocorticism or with evidence of progressive malignant neoplasia, as the active substance has not been evaluated in these cases.

Precautions:	APOQUEL (oclacitinib) modulates the immune system. APOQUEL may increase the susceptibility to infection and the development of papillomas, and may exacerbate neoplastic conditions including subclinical neoplastic conditions. Dogs receiving APOQUEL should therefore be monitored for the development of infections and neoplasia. The safety of the drug has not been studied in breeding male dogs, nor in pregnant or lactating female dogs. In the absence of such studies, it is not recommended to use the drug in pregnant or lactating bitches or in dogs intended for breeding. APOQUEL is not for use in dogs less than 12 months of age or less than 3 kg bodyweight. The use of Apoquel has not been evaluated in combination with glucocorticoids,cyclosporine, or other systemic immunosuppressive agents.

Side Effects:	Treatment of pruritus associated with allergic dermatitis: In two overseas field studies, a total of 321 dogs received 0.4 – 0.6 mg/kg of APOQUEL twice daily for 14 days. There were no serious adverse events reported during both studies. The most reported abnormal clinical signs were vomiting and diarrhoea. The commonly (>1 but < 10 in 100 treated animals) abnormal clinical signs were: vomiting, diarrhoea, anorexia, polydipsia, polyphagia, lethargy, pruritus, otitis externa and dermatitis. APOQUEL related clinical pathology changes noted over the course of the study included a slight decrease in white blood cells (neutrophil, eosinophil, and monocyte counts) which remained within the normal reference range. Lymphocyte count for the APOQUEL treated group appeared to increase at Day 7, but returned to pretreatment levels with on-going treatment by end of study. Serum cholesterol increased in 25% of APOQUEL dogs, but the mean and individual values remained within the reference range. Elevated liver enzymes (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase) occurred at similar incidence rates in the APOQUEL and placebo-treated groups during the study. Treatment of clinical manifestations of atopic dermatitis in dogs: In an overseas study to demonstrate the field efficacy and safety of APOQUEL for the treatment of the clinical manifestations of atopic dermatitis, 155 dogs received 0.4 – 0.6 mg/kg of APOQUEL twice daily for 14 days, then once daily for maintenance therapy. During the first 30 days of the blinded field trial, the most frequently reported abnormal clinical signs (> 1 but < 10 in 100 treated animals) were pyoderma, diarrhoea, emesis, dermatitis, otitis, anorexia and lethargy. After day 16, abnormal clinical signs, in addition to those clinical signs listed above and occurring in greater than 1% of the dogs receiving oclacitinib included non-specified dermal lumps, pododermatitis, lymphadenopathy, aggression, and the development of papillomas. Beyond day 30, abnormal clinical signs in addition to those clinical signs listed above and occurring in greater than 1% of the dogs receiving APOQUEL included histiocytoma, cystitis, dermatomycosis, lipoma (palpable mass), urinary incontinence, urinary tract infection and hypothyroidism. APOQUEL related clinical pathology changes were restricted to a small increase in mean serum cholesterol and a small decrease in mean leukocyte count. The small decrease in mean leukocyte count observed in oclacitinib-treated dogs was not progressive, and affected all white blood cell counts (neutrophil, eosinophil, and monocyte counts) except lymphocyte counts; all mean values remained within the laboratory reference range. Neither of these clinical pathology changes appeared clinically significant. If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon or Zoetis Australian Technical Services Toll Free on 1800 814 883.

Dosage and Administration:	READ THE PACKAGE LEAFLET BEFORE USE Each tablet contains 3.6 mg, 5.4 mg or 16 mg oclacitinib as oclacitinib maleate. Each tablet is scored and marked with AQ and either an S, M, or L that correspond to the different tablet strengths on both sides. PRESENTATION APOQUEL is available in bottles containing 20 or 100 tablets of 3.6, 5.4 or 16 mg oclacitinib. OR APOQUEL is available in blister packs containing 20 or 100 tablets of 3.6, 5.4 or 16 mg oclacitinib. For oral use.

	The dose of APOQUEL (oclacitinib maleate) is 0.4 - 0.6 mg/kg bodyweight, administered twice daily for up to 14 days, and then administered once daily for maintenance therapy. Please see dosing table below for number of tablets required. Tablets are breakable along the score line on the tablet. Weight Range (in kg) Number of tablets to be administered Low High 3.6 mg 5.4 mg 16 mg 3.0 4.4 0.5 - - 4.5 5.9 - 0.5 - 6.0 8.9 1 - - 9.0 13.4 - 1 - 13.5 19.9 - - 0.5 20.0 26.9 - 2 - 27.0 39.9 - - 1 40.0 54.9 - - 1.5 55.0 80.0 - - 2 Tablets can be administered with or without food. Overdose: APOQUEL was administered to healthy, one year old Beagle dogs twice daily for 6 weeks, followed by once per day for 20 weeks, at 0.6 mg/kg (1X), 1.8 mg/kg (3X) and 3.0 mg/kg (5X) for a total of 26 weeks. Clinical observations that were considered likely to be related to oclacitinib treatment included: alopecia (local), papilloma, dermatitis, erythema, abrasions & scabbing/crusts, interdigital “cysts”, and oedema of feet. Dermatitis lesions were mostly secondary to the development of interdigital furunculosis on one or more feet during the study with the number and frequency of observations increasing with increasing dose. Lymphadenopathy of peripheral nodes was noted in all groups, increased in frequency with increasing dose and was frequently associated with interdigital furunculosis. Papilloma was considered treatment related but not dose related. There is no specific antidote and in case of signs of overdose the dog should be treated symptomatically.

General Directions:	Dogs should be carefully observed following administration to ensure that each tablet is swallowed. Clinical Pharmacology Mechanism of Action Oclacitinib inhibits the function of a variety of pruritogenic cytokines and pro-inflammatory cytokines, as well as cytokines involved in allergy that are dependent on JAK1 or JAK3 enzyme activity, whereas it has little effect on cytokines involved in haematopoiesis that are dependent on JAK2. However, oclacitinib may also exert effects on other cytokines with the potential for unwanted effects. Oclacitinib is not a corticosteroid or an antihistamine. Pharmacokinetics In dogs, oclacitinib maleate is rapidly and well absorbed following oral administration, with LS-mean time to peak plasma concentrations (tmax) of less than 1 hour. The absolute bioavailability of oclacitinib maleate was 89%. The prandial state of dogs does not significantly affect the rate or extent of absorption. Total body oclacitinib clearance from plasma was low – 316 ml/h/kg bodyweight (5.3 ml/min/kg bodyweight), and the apparent volume of distribution at steady-state was 942 ml/kg bodyweight. Following IV and PO administration, the terminal t1/2 appeared similar with values of 3.5 and 4.1 hours, respectively. Oclacitinib has low protein binding with 66.3 -69.7% bound in fortified canine plasma at nominal concentrations ranging from 10 -1000

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Clinical Pharmacology

Mechanism of Action

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Oclacitinib is not a corticosteroid or an antihistamine.

Pharmacokinetics

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Oclacitinib is metabolized in the dog to multiple metabolites and one major oxidative metabolite was identified in plasma and urine.

Overall the major clearance route is metabolism with minor contributions from renal and biliary elimination. Inhibition of canine cytochrome P450s by Apoquel is minimal with IC50s 50 fold greater than the observed mean Cmax (333 ng/ml or 0.997 μM) following 0.6 mg/kg oral administration in the target animal safety study. Therefore, the risk of metabolic drug-drug interactions due to oclacitinib inhibition is very low. No accumulation was observed in blood of dogs treated for 6 months.

When treating pruritus associated with allergic dermatitis with oclacitinib, investigate and treat any underlying causes (e.g. flea allergic dermatitis, contact dermatitis, food hypersensitivity). Furthermore, in cases of allergic dermatitis and atopic dermatitis, it is recommended to investigate and treat complicating factors, such as bacterial (e.g. otitis externa, pyoderma), fungal or parasitic infections/infestations (e.g. flea and mange).

Given the potential for effects on certain clinicopathological parameters, periodic monitoring with complete blood counts and serum biochemistry is recommended when dogs are on treatment long-term.

Treatment of pruritus associated with allergic skin disease often requires a multimodal approach. This may include the use of Allergen Specific Immunotherapy (ASIT).

No drug interactions were observed in field studies where oclacitinib was administered concomitantly with veterinary medicinal products such as endo- and ectoparasiticides, antimicrobials and anti-inflammatories.

The impact of oclacitinib administration on vaccination with modified live vaccines, canine parvovirus (CPV), canine distemper virus (CDV) and canine parainfluenza (CPI), on 16 week old vaccine naïve puppies has been studied. An adequate immune response (serology) to CDV and CPV vaccination was achieved when puppies were administered oclacitinib at 1.8 mg/kg bodyweight (bw) twice daily for 84 days. However, the findings of this study indicated a reduction in serological response to vaccination with CPI in puppies being treated with oclacitinib compared to untreated controls. The clinical relevance of

	these observed effects for animals vaccinated while being administered oclacitinib (in accordance with the recommended dosing regimen) is unclear.

Withholding Periods:	

Trade Advice:	

Safety Directions:	Will irritate the eyes. Avoid contact with eyes. Wash hands after use. Precautionary statement: Accidental ingestion of oclacitinib can be harmful for children. To avoid accidental ingestion, administer the tablet to the dog immediately after removal from the package. Keep out of reach and sight of children.

First Aid Instructions:	If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126.

First Aid Warnings:	

Additional User Safety:	Refer to the material safety data sheet.

Environmental Statements:	

Disposal:	Dispose of container by wrapping with paper and putting in garbage

Storage:	Store below 30°C (Room temperature) In-use shelf life: Half-tablets should be stored in the provided bottle with cap sealed. Use ½ tablets within 14 days. OR In-use shelf life: Half-tablets should be placed back in the opened blister and returned to the carton. Use ½ tablets within 3 days.