▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

WARNINGS:

Based on the results from a post-marketing safety study of another JAK inhibitor, CIBINQO should only be used if no suitable treatment alternatives are available in patients:

- With history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers).
- With malignancy risk factors (e.g., current malignancy or history of malignancy).
- Who are 65 years of age and older.

See Section 4.4 Special Warnings and Precautions for Use: Mortality; Major Adverse Cardiovascular Events (MACE); Thrombosis, Malignancy, Non-melanoma Skin Cancer and Use in the Elderly.

AUSTRALIAN PRODUCT INFORMATION – CIBINQO® (ABROCITINIB) TABLETS

1. NAME OF THE MEDICINE

Abrocitinib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CIBINQO film coated tablets contain 50 mg, 100 mg, or 200 mg of abrocitinib.

Contains lactose. For the full list of excipients, see Section 6.1, List of excipients.

3. PHARMACEUTICAL FORM

Film coated tablet.

CIBINQO® 50 mg film coated tablets

Pink, oval tablet, debossed with “PFE” on one side and “ABR 50” on the other.

CIBINQO® 100 mg film coated tablets

Pink, round tablet, debossed with “PFE” on one side and “ABR 100” on the other.

CIBINQO® 200 mg film coated tablets

Pink, oval tablet, debossed with “PFE” on one side and “ABR 200” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CIBINQO is indicated for the treatment of moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy. CIBINQO can be used with or without medicated topical therapies for atopic dermatitis.

4.2 Dose and method of administration

CIBINQO treatment should be initiated and supervised by a dermatologist or physician specialising in treatment of atopic dermatitis.

Dosage

Treatment with CIBINQO should only be considered if the treatment benefit outweighs the associated risks (see Section 4.4 Special warnings and precautions for use).

The recommended starting dose is 100 mg or 200 mg once daily based on individual patient characteristics:

- A starting dose of 100 mg once daily is recommended for patients at higher risk of venous thromboembolism (VTE), major adverse cardiovascular event (MACE) and malignancy (see Section 4.2 Dosage adjustment, Section 4.4 Special warnings and precautions for use).

- A dose of 200 mg once daily may be appropriate for patients with high disease burden who are not at higher risk of VTE, MACE and malignancy or for patients with an inadequate response to 100 mg once daily. Upon disease control, dose should be decreased to 100 mg once daily. If disease control is not maintained after dose reduction, re-treatment with 200 mg once daily can be considered.

The lowest effective dose for maintenance should be considered.

Discontinuation of treatment should be considered in patients who show no evidence of therapeutic benefit after 24 weeks.

CIBINQO can be used with or without medicated topical therapies for atopic dermatitis.

Laboratory monitoring

Table 1. Laboratory measures and monitoring guidance

Laboratory measures	Monitoring guidance	Action
Complete blood count including Platelet Count, Absolute Lymphocyte Count (ALC), Absolute Neutrophil Count (ANC) and Haemoglobin (Hb)	Before treatment initiation, 4 weeks after initiation and thereafter according to routine patient management.	Platelets: Treatment should be discontinued if platelet counts are < 50,000 /mm^3.
		ALC: Treatment should be interrupted if ALC is < 500 /mm^3 and may be restarted once ALC returns above this value. Treatment should be discontinued if confirmed.
		ANC: Treatment should be interrupted if ANC is < 1000 /mm^3 and may be restarted once ANC returns above this value.
		Hb: Treatment should be interrupted if Hb is < 8 g/dL and may be restarted once Hb returns above this value.
Lipid parameters	Before treatment initiation, 4 weeks after initiation and thereafter according to the patient's risk for cardiovascular disease and clinical guidelines for hyperlipidaemia.	Patients should be monitored according to clinical guidelines for hyperlipidaemia.

Treatment initiation

Treatment with CIBINQO should not be initiated in patients with a platelet count <150,000 /mm^3, an absolute lymphocyte count (ALC) <500 /mm^3, an absolute neutrophil count (ANC) <1000 /mm^3 or who have a haemoglobin value <8 g/dL (see Section 4.4 Special warnings and precautions for use).

Dose interruption

If a patient develops a serious infection, sepsis or opportunistic infection, consider interruption of CIBINQO until the infection is controlled (see Section 4.4 Special warnings and precautions for use).

Interruption of dosing may be needed for management of laboratory abnormalities as described in Table 1.

Missed doses

If a dose is missed, patients should be advised to take the dose as soon as possible unless it is less than 12 hours before the next dose, in which case the patient should not take the missed dose. Thereafter, resume dosing at the regular scheduled time.

Dosage adjustment

Drug-drug interactions

50 mg once daily is the recommended dose for patients taking strong inhibitors of cytochrome P450 (CYP) 2C19 (e.g., fluvoxamine, fluconazole), 100 mg once daily should only be

considered for those patients who are not responding to 12 weeks of treatment with 50 mg once daily. Please refer above for dosing regimen.

The use of CIBINQO is not recommended concomitantly with strong inducers of CYP enzymes (e.g., rifampin) (see Section 4.5 Interactions with other medicines and other forms of interactions).

Renal impairment

No dose adjustment is required in patients with mild renal impairment, i.e., estimated glomerular filtration rate (eGFR) of 60 to <90 mL/min.

50 mg once daily is the recommended dose for patients with moderate (eGFR 30 to <60 mL/min) or severe (eGFR <30 mL/min) renal impairment. 100 mg once daily should only be considered for those patients who are not responding to 12 weeks of treatment with 50 mg once daily. Please refer above for dosing regimen (see Section 5.2 Pharmacokinetic properties).

The use of CIBINQO has not been studied in patients with end-stage renal disease (ESRD) on renal replacement therapy.

Hepatic impairment

CIBINQO must not be used in patients with severe (Child-Pugh C) hepatic impairment (see Section 4.3 Contraindications).

No dose adjustment is required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment (see Section 5.2 Pharmacokinetic properties).

Elderly population

The recommended starting dose for patients ≥ 65 years of age is 100 mg once daily (See Section 4.4 Special warnings and precautions for use).

Paediatric population

See Section 4.8 Adverse effects (undesirable effects).

Method of administration

CIBINQO is to be taken orally once daily with or without food at approximately the same time each day.

In patients who experience nausea while taking CIBINQO, taking with food may improve nausea.

Swallow CIBINQO tablets whole and intact with water. Do not crush, split, or chew CIBINQO tablets.

4.3 Contraindications

- CIBINQO is contraindicated in patients taking antiplatelet therapies, except for low-dose aspirin (<81 mg daily), during the first 3 months of treatment (See section 4.5 Interactions with other medicines and other forms of interactions).
- CIBINQO must not be used in combination with biological disease-modifying anti-rheumatic drugs (bDMARDs).
- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of excipients.
- Active serious systemic infections, including tuberculosis (TB) (see Section 4.4 Special warnings and precautions for use).
- Severe hepatic impairment (see Section 4.2 Dose and method of administration).
- Pregnancy and lactation (see Section 4.6 Fertility, pregnancy and lactation).

4.4 Special warnings and precautions for use

Mortality

In a large, randomised, post-marketing safety study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years of age and older with at least one additional cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with tofacitinib compared to TNF inhibitors. Mortality was mainly due to cardiovascular events, infections and malignancies.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with CIBINQO (see Boxed Warnings and section 4.4 Special warnings and precautions for use; MACE, Thrombosis, Malignancy (including non-melanoma skin cancers), Serious Infections and Use in the Elderly).

Major Adverse Cardiovascular Events (MACE)

Events of MACE have been observed in patients taking CIBINQO (See Section 4.8 Adverse effects (undesirable effects)).

In a large randomised post-marketing safety study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE), defined as cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke, was observed with tofacitinib compared to TNF inhibitors. MACE, including events of myocardial infarction, were more common in older patients and in patients who were current or past smokers.

Therefore, in patients 65 years of age and older, patients who are current or past long-time smokers, atherosclerotic cardiovascular disease or other cardiovascular risk factors, CIBINQO should only be used if no suitable treatment alternatives are available.

Thrombotic events including pulmonary embolism

Serious and sometimes fatal events of thrombosis, including deep venous thrombosis (DVT), arterial thrombosis and pulmonary embolism (PE) have occurred in patients treated with JAK inhibitors including CIBINQO (see Section 4.8 Adverse effects (undesirable effects)).

A higher rate of VTE was observed with abrocitinib 200 mg compared to abrocitinib 100 mg (see Section 4.8 Adverse effects (undesirable effects)).

In a large randomised post-marketing safety study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a dose dependent higher rate of VTE including deep venous thrombosis (DVT) and pulmonary embolism (PE) was observed with tofacitinib compared to TNF inhibitors.

In patients with cardiovascular or malignancy risk factors (see Section 4.4 Special warnings and precautions for use; Major adverse cardiovascular events (MACE) and Malignancy (including non- non-melanoma skin cancers)), CIBINQO should only be used if no suitable treatment alternatives are available.

Avoid CIBINQO in patients with an increased risk of thrombosis or in whom risk factors are identified.

Risk factors other than cardiovascular or malignancy risks factors that should be considered in determining the patient's risk for DVT/PE include older age, obesity, a medical history of DVT/PE, prothrombotic disorder, use of combined hormonal contraceptives or hormone replacement therapy, patients undergoing major surgery, or prolonged immobilisation.

Patients should be re-evaluated periodically during CIBINQO treatment to assess for changes in VTE risk.

Promptly evaluate patients with signs and symptoms of VTE and discontinue CIBINQO in patients with suspected VTE, regardless of dose or indication.

Across all subjects treated with abrocitinib, there were 3 non-fatal adjudicated events of pulmonary embolism (0.14/100 patient-years [95% CI: 0.03, 0.41]) and all of these occurred in subjects on abrocitinib 200 mg QD. All these 3 subjects were discontinued from the study treatment and had recovered from the event. Three non-fatal adjudicated events of deep venous thrombosis (0.14/100 PY [95% CI: 0.03, 0.41]) were also observed, all in the 200 mg QD group (see Section 4.8 Adverse effects (undesirable effects)).

Malignancy (including non-melanoma skin cancers)

Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including CIBINQO.

Malignancies, including non-melanoma skin cancer (NMSC), were observed in clinical studies with CIBINQO. Clinical data are insufficient to assess the potential relationship of exposure to CIBINQO and the development of malignancies. Long-term safety evaluations are ongoing.

In clinical studies with CIBINQO, a higher rate of malignancy (excluding non-melanoma skin cancer, NMSC) was observed with abrocitinib 200 mg compared to abrocitinib 100 mg (see Section 4.8 Adverse effects (undesirable effects)).

In a large randomised post-marketing safety study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of malignancies, particularly lung cancer, lymphoma and non-melanoma skin cancer (NMSC) was observed with tofacitinib compared to TNF inhibitors. In patients 65 years of age and older, patients who are current or past long-time smokers, or with other malignancy risk factors (e.g. current malignancy or history of malignancy), CIBINQO should only be used if no suitable treatment alternatives are available.

The risks and benefits of CIBINQO treatment should be considered prior to initiating in patients with a known malignancy.

Periodic skin examination is recommended for all patients, particularly those who are at increased risk for skin cancer.

Serious infections

Serious infections have been reported in patients receiving CIBINQO. The most frequent serious infections in clinical studies were herpes simplex, herpes zoster, and pneumonia (see Section 4.8 Adverse effects (undesirable effects)).

Serious infections leading to hospitalisation or death have been reported in patients receiving JAK inhibitors used to treat inflammatory conditions.

Treatment must not be initiated in patients with an active, serious systemic and localised infection (see Section 4.3 Contraindications).

Risks and benefits of treatment prior to initiating CIBINQO should be considered for patients:

- with chronic or recurrent infection
- who have been exposed to Tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or travelled in areas of endemic TB or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with CIBINQO. Interrupt CIBINQO if the patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with CIBINQO should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient and appropriate antimicrobial therapy should be initiated. The patient should be closely monitored and CIBINQO therapy should be temporarily interrupted if the patient is not responding to standard therapy.

Tuberculosis

Patients should be screened for TB before starting CIBINQO therapy. Yearly screening for patients in highly endemic areas for TB should be considered. CIBINQO must not be given to patients with active TB (see Section 4.3 Contraindications). For patients with a new diagnosis of latent TB or prior untreated latent TB, preventive therapy for latent TB should be started prior to initiation of CIBINQO. Monitor patients for the development of signs and symptoms of TB, including patients who were tested negative for latent TB infection prior to initiating therapy.

Viral reactivation

Viral reactivation, including herpes virus reactivation (e.g., herpes zoster, herpes simplex), was reported in clinical studies (see Section 4.8 Adverse effects (undesirable effects)). The rate of herpes zoster infections was higher in patients 65 years of age and older and patients with severe atopic dermatitis at baseline (see Section 4.8 Adverse effects (undesirable effects)). If a patient develops herpes zoster, temporary interruption of treatment should be considered until the episode resolves.

Eczema herpeticum (disseminated viral infection mostly due to herpes simplex virus) was also reported in clinical studies with abrocitinib. The condition is characterised by rapid spread of vesicular and erosive lesions, fever and malaise in patients with atopic dermatitis and requires prompt treatment with antiviral agents. Discontinuation or interruption of abrocitinib therapy until the resolution of an eczema herpeticum infection should be considered, depending on the seriousness of the event.

Hepatitis B virus (HBV) reactivation has been reported in patients receiving JAK inhibitors. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy and during therapy with CIBINQO. Patients with evidence of active hepatitis B or hepatitis C (positive hepatitis C PCR) infection were excluded from clinical studies (see Section 5.2 Pharmacokinetic properties). Patients who were hepatitis B surface antigen negative, hepatitis B core antibody positive, and hepatitis B surface antibody positive had testing for hepatitis B virus (HBV) DNA. Patients who had HBV DNA above the lower limit of quantification (LLQ) were excluded. Patients who had HBV DNA negative or below LLQ could initiate treatment with CIBINQO; such patients had HBV DNA monitored. If HBV DNA is detected, a liver specialist should be consulted.

Vaccination

No data are available on the response to vaccination in patients receiving CIBINQO. Use of live, attenuated vaccines should be avoided during or immediately prior to CIBINQO. Prior to initiating CIBINQO, it is recommended that patients be brought up to date with all immunisations, including prophylactic herpes zoster vaccinations, in agreement with current immunisation guidelines.

Haematologic abnormalities

Confirmed ALC <500/mm^3 and platelet count <50,000/mm^3 were observed in less than 0.5% of patients in clinical studies (see Section 4.8 Adverse effects (undesirable effects)). Treatment with CIBINQO should not be initiated in patients with a platelet count <150,000/mm^3, an ALC <500/mm^3, an ANC <1000/mm^3 or who have a haemoglobin value <8 g/dL (see Section 4.2 Dose and method of administration). Platelet count and ALC should be monitored 4 weeks after initiation of therapy with CIBINQO and thereafter according to routine patient management (see Table 1 in Section 4.2 Dose and method of administration).

Subjects with current or past medical history of conditions associated with thrombocytopenia, coagulopathy or platelet dysfunction and receiving anti-coagulants or medications known to cause thrombocytopenia were not evaluated in the abrocitinib clinical studies.

Lipids

Dose-dependent increase in blood lipid parameters were reported in patients treated with CIBINQO compared to placebo (see Section 4.8 Adverse effects (undesirable effects)). Lipid

parameters should be assessed approximately 4 weeks following initiation of CIBINQO therapy and thereafter according to their risk for cardiovascular disease. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined. Patients with abnormal lipid parameters should be further monitored and managed according to clinical guidelines, due to the known cardiovascular risks associated with hyperlipidaemia. In patients with a high burden of cardiovascular risk factors, the risks and benefits of CIBINQO compared to that of other available therapies for atopic dermatitis should be considered. If CIBINQO is chosen, interventions to manage lipid concentrations should be implemented according to clinical guidelines.

Use in the elderly

Considering the increased risk of MACE, malignancies, serious infections and all-cause mortality in patients 65 years and older, as observed in a large randomised post-marketing study of tofacitinib (another JAK inhibitor), CIBINQO should only be used in these patients if no suitable treatment alternatives are available.

A total of 145 patients 65 years of age and older were enrolled in CIBINQO studies. A higher proportion of patients 65 years of age and older discontinued from clinical studies and were more likely to have serious adverse events compared to younger patients; patients 65 years and older were more likely to develop low platelet and ALC values; the incidence rate of herpes zoster in patients 65 years of age and older was higher than that of younger patients (see Section 4.8 Adverse effects (undesirable effects)).

There are limited data in patients above 75 years of age.

Immunosuppressive medicinal products

Combination with biologic immunomodulators, potent immunosuppressants such as ciclosporin or other Janus kinase (JAK) inhibitors has not been studied. Their concomitant use with abrocitinib is not recommended as a risk of additive immunosuppression cannot be excluded (see Section 4.3 Contraindications).

4.5 Interactions with other medicines and other forms of interactions

Potential for other medicines to affect pharmacokinetics of abrocitinib

Abrocitinib is metabolised predominantly by CYP2C19 and CYP2C9 enzymes, and its active metabolites are renally excreted and are substrates of the organic anion transporter 3 (OAT3). Therefore, exposures of abrocitinib and/or its active metabolites may be affected by medicinal products that strongly inhibit or induce CYP2C19 or CYP2C9 or inhibit the OAT3 transporter. Dose adjustments, as appropriate, based on these results are outlined in Section 4.2 Dose and method of administration.

Coadministration with CYP2C19/CYP2C9 inhibitors

When CIBINQO 100 mg was administered concomitantly with fluvoxamine (a strong CYP2C19 and moderate CYP3A inhibitor) or fluconazole (a strong CYP2C19, moderate CYP2C9 and CYP3A inhibitor), the extent of exposure of abrocitinib active moiety increased by 91% and 155%, respectively, compared with administration alone.

Coadministration with CYP2C19/CYP2C9 inducers

Administration of CIBINQO 200 mg after multiple dosing with rifampin, a strong inducer of CYP enzymes, resulted in reduction of abrocitinib active moiety exposures by approximately 56%.

Coadministration with OAT3 inhibitors

When CIBINQO 200 mg was administered concomitantly with probenecid, an OAT3 inhibitor, abrocitinib active moiety exposures increased by approximately 66%. This is not clinically significant, and a dose adjustment is not needed.

Potential for abrocitinib to affect pharmacokinetics of other medicines

In vitro, abrocitinib or its metabolites were not significant inhibitors or inducers of most CYPs (CYP1A2, CYP2B6, CYP2C8 and CYP2C9 or of uridine diphosphate-glucuronyltransferases (UGTs) (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7). *In vitro*, abrocitinib was an inhibitor of intestinal P-glycoprotein (P-gp), organic anion transporter (OAT)3, organic cation transporter (OCT)1, multidrug and toxin compound extrusion protein (MATE)1/2K and breast cancer resistance protein (BCRP) but is not an inhibitor of organic anion transporting polypeptide (OATP)1B1/1B3, bile salt export pump (BSEP), OAT1 or OCT2 at clinically meaningful concentrations. The metabolites do not change the transporter inhibition risk compared to abrocitinib. *In vitro*, abrocitinib was a mechanism-based inhibitor of CYP2C19 and CYP2D6.

While in vitro studies indicated that abrocitinib was a mechanistic-based inhibitor of CYP3A4/5, no clinically significant effects of CIBINQO were observed in drug interaction studies with oral contraceptives (e.g., ethinyl estradiol/levonorgestrel), or with substrates of BCRP and OAT3 (e.g., rosuvastatin), MATE1/2K (e.g., metformin) and CYP3A4 (e.g., midazolam). Coadministration of dabigatran etexilate (a P-gp substrate), with a single dose of CIBINQO 200 mg increased dabigatran AUC_{inf} and C_{max} by approximately 53% and 40%, respectively, compared with administration alone.

Antiplatelet therapy drugs

Coadministration of CIBINQO with antiplatelet therapy drugs may increase the risk of bleeding with thrombocytopenia. Antiplatelet drugs, except for low-dose aspirin (≤81 mg daily), during the first 3 months of treatment are contraindicated with CIBINQO (see Section 4.3 Contraindications).

4.6 Fertility, pregnancy and lactation

Effects on fertility

Fertility was unaffected in male rats treated orally with 70 mg/kg/day abrocitinib (29 times the exposures of the unbound AUC at the maximum recommended human dose (MRHD) of 200 mg. However, lower fecundity and fertility indices (50%) were observed in females treated with the same dose which was reversible 1 month after cessation of treatment. Female fertility was unaffected at 10 mg/kg/day (2 times the exposures of the unbound AUC at the MRHD of 200 mg).

Use in pregnancy – Pregnancy Category D

The limited human data on use of abrocitinib in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage.

In embryofetal development studies, oral administration of abrocitinib to pregnant rats during organogenesis resulted in fetal skeletal variations (short and thickened ribs, un-ossified metatarsals and cervical arches with reduced ventral processes) at ≥ 30 mg/kg/day (exposures at the no observed adverse effect level (NOAEL) equal to 2.4 times the unbound AUC at the maximum recommended human dose (MRHD) of 200 mg clinical dose). In embryofetal development studies, oral administration of abrocitinib to pregnant rabbits resulted in skeletal variations (not ossified sternal centra and forelimb phalanx) at ≥10 mg/kg/day (subclinical exposures of the unbound AUC at the MRHD of 200 mg once daily). In a pre- and postnatal development study in pregnant rats, abrocitinib oral administration during gestation and through lactation, dams had difficulty delivering and lower postnatal survival and lower offspring body weights were seen at ≥ 30 mg/kg/day (exposures at the NOAEL approximately 2.4 times the unbound AUC at the MRHD of 200 mg once daily. CIBINQO is contraindicated during pregnancy (see Section 4.3 Contraindications).

Use in lactation

There are no data on the presence of abrocitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Abrocitinib was secreted in milk of lactating rats. A risk to newborns/infants cannot be excluded and CIBINQO is contraindicated during breastfeeding (see Section 4.3 Contraindications).

Women of childbearing potential

Women of reproductive potential should be advised to use effective contraception during treatment and for 1 month following the final dose of CIBINQO. Pregnancy planning and prevention for females of reproductive potential should be encouraged.

4.7 Effects on ability to drive and use machines

CIBINQO has no or negligible influence on the ability to drive and use machines.

4.8 Adverse effects (undesirable effects)

Adverse Events Reported in Clinical Trials

A total of 3,128 patients, representing 2,089 patient-years of exposure, were treated with CIBINQO in 7 clinical studies in atopic dermatitis including the long-term extension study. There were 994 patients with at least 48 weeks of exposure CIBINQO. Five placebo-controlled studies were integrated (703 patients on 100 mg once daily, 684 patients on 200 mg once daily and 438 patients on placebo) to evaluate the safety of CIBINQO in comparison to placebo for up to 16 weeks. Three studies were conducted with CIBINQO as monotherapy and 2 studies were conducted with CIBINQO in combination with other topical medications.

Table 3 Summary of Adverse Events reported by >2% of patients treated with either dose of CIBINQO (all causalities) – double-blind, placebo-controlled monotherapy studies up to 12 weeks.

	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg
	(N=211)	(N=370)	(N=364)
System Organ Class Preferred Term	**n (%)**	**n (%)**	**n (%)**
Gastrointestinal Disorders			
Diarrhoea	1 (0.5)	1 (0.3)	8 (2.2)
Nausea	2 (0.9)	21 (5.7)	53 (14.6)
Vomiting	0	4 (1.1)	9 (2.5)
Infections and Infestations			
Nasopharyngitis	3 (1.4)	9 (2.4)	2 (0.5)
Nervous System Disorders			
Headache	4 (1.9)	12 (3.2)	19 (5.2)
Skin and Subcutaneous Tissue Disorders			
Dermatitis atopic	10 (4.7)	6 (1.6)	3 (0.8)

Table 4 Summary of Adverse Events reported by >2% of patients treated with either dose of CIBINQO (all causalities) – double-blind, placebo-controlled combination studies up to 16 weeks.

	Placebo (N=227)	Abrocitinib 100 mg (N=333)	Abrocitinib 200 mg (N=320)
System Organ Class Preferred Term	**n (%)**	**n (%)**	**n (%)**
Gastrointestinal Disorders			
Nausea	3 (1.3)	17 (5.1)	42 (13.1)
Vomiting	1 (0.4)	5 (1.5)	8 (2.5)
Infections and Infestations			
Folliculitis	5 (2.2)	11 (3.3)	6 (1.9)
Herpes simplex	1 (0.4)	5 (1.5)	9 (2.8)
Nasopharyngitis	18 (7.9)	30 (9.0)	23 (7.2)
Pharyngitis	4 (1.8)	7 (2.1)	4 (1.3)
Upper respiratory tract infection	16 (7.0)	21 (6.3)	19 (5.9)
Urinary tract infection	3 (1.3)	4 (1.2)	7 (2.2)
Investigations			
Blood creatine phosphokinase increased	3 (1.3)	11 (3.3)	10 (3.1)
Nervous System Disorders			
Dizziness	3 (1.3)	4 (1.2)	13 (4.1)
Headache	13 (5.7)	15 (4.5)	23 (7.2)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	4 (1.8)	7 (2.1)	5 (1.6)
Skin and Subcutaneous Tissue Disorders			
Acne	1 (0.4)	10 (3.0)	20 (6.3)
Dermatitis atopic	8 (3.5)	9 (2.7)	4 (1.3)

Adverse reactions

The most commonly reported adverse reactions occurring in ≥ 2% of patients treated with CIBINQO 200 mg in placebo-controlled studies are nausea (15.1%), headache (7.9%), acne

(4.8%), herpes simplex (4.2%), blood creatine phosphokinase increased (3.8%), vomiting (3.5%), dizziness (3.4%) and abdominal pain upper (2.2%). The most frequent serious adverse reactions are infections (0.3%) (see Section 4.4 Special warnings and precautions for use).

Table 5. Adverse reactions

System organ class	Very common	Common	Uncommon
Infections and infestations		Herpes simplex[a] Herpes zoster[b]	
Blood and lymphatic system disorders			Thrombocytopenia Lymphopenia
Metabolism and nutrition disorders			Hyperlipidaemia[c]
Nervous system disorders		Headache Dizziness	
Vascular disorders			Venous thrombotic events including pulmonary embolism[d]
Gastrointestinal disorders	Nausea	Vomiting Abdominal pain upper	
Skin and subcutaneous tissue disorders		Acne	
Investigations		Creatine phosphokinase increased > 5 × ULN[e]	

a. Herpes simplex includes oral herpes, ophthalmic herpes simplex, genital herpes, and herpes dermatitis.
b. Herpes zoster includes ophthalmic herpes zoster.
c. Hyperlipidaemia includes dyslipidaemia and hypercholesterolaemia.
d. Venous thrombotic events include deep vein thrombosis.
e. Includes changes detected during laboratory monitoring (see text below).

Description of selected adverse reactions

Infections

In placebo-controlled studies, for up to 16 weeks, infections have been reported in 27.4% of patients treated with placebo and in 34.9% and 34.8% of patients treated with CIBINQO 100 mg and 200 mg, respectively. Most infections were mild or moderate. The percentage of patients reporting infection-related adverse drug reactions in the 200 mg and 100 mg groups compared to placebo were: herpes simplex (4.2% and 2.8% vs 1.4%), herpes zoster (1.2% and 0.6% vs 0%), pneumonia (0.1% and 0.1% vs 0%). Herpes simplex was more frequent in patients with a history of herpes simplex or eczema herpeticum. Most of the herpes zoster events involved a single dermatome and were non-serious. All the opportunistic infections were cases of multidermatomal cutaneous herpes zoster (0.6%), most of which were non-serious. The incidence rate of herpes zoster in patients 65 years of age and older (7.40 per 100 patient-years) was higher than that of patients 18 to less than 65 years of age (3.44 per 100 patient-years) and less than 18 years of age (2.12 per 100 patient-years). The incidence rate of herpes zoster in patients with severe atopic dermatitis at baseline (4.93 per 100 patient- years) was higher than that of patients with moderate atopic dermatitis at baseline (2.49 per 100 patient-years) (see Section 4.4 Special warnings and precautions for use).

In placebo-controlled studies, for up to 16 weeks, the rate of serious infections was 1.81 per 100 patient-years in patients treated with placebo, 3.32 per 100 patient-years in patients treated with 100 mg, and 1.12 per 100 patient-years in patients treated with 200 mg. Among all patients treated with CIBINQO including the long-term extension study, the rate of serious infections was 2.65 per 100 patient-years treated with 100 mg and 2.33 per 100 patient-years

treated with 200 mg. The most commonly reported serious infections were herpes simplex, herpes zoster, and pneumonia (see Section 4.4 Special warnings and precautions for use).

Venous thrombotic events including pulmonary embolism

Among all patients treated with CIBINQO, including the long-term extension study, the rate of PE was 0.23 per 100 patient-years for 200 mg and 0 per 100 patient-years for 100 mg. The rate of DVT was 0.23 per 100 patient-years in the 200 mg group and 0 per 100 patient years in the 100 mg group (see Section 4.4 Special warnings and precautions for use).

Malignancy (excluding non-melanoma skin cancers)

In clinical studies with CIBINQO, the incidence of malignancies (excluding non-melanoma skin cancers) reported in the 100 mg and 200 mg abrocitinib arms (incidence rate [95% confidence interval], /100 patient-years) were 0.15 (0.03, 0.43) and 0.34 (0.17, 0.60), respectively.

Thrombocytopenia

In placebo -controlled studies, for up to 16 weeks, treatment was associated with a dose-related decrease in platelet count. Maximum effects on platelets were observed within 4 weeks, after which the platelet count returned towards baseline despite continued therapy. Confirmed platelet counts of < 50,000/mm^3 were reported in 0.1% of patients exposed to 200 mg, and in 0 patients treated with 100 mg or placebo. Among all patients exposed to CIBINQO, including the long-term extension study, confirmed platelet counts of < 50,000/mm^3 were reported in 0.1% of patients treated with 200 mg, occurring at Week 4. A higher proportion of patients 65 years of age and older developed a platelet count nadir < 75, 000/mm^3 (see Section 4.4 Special warnings and precautions for use).

Lymphopenia

In placebo-controlled studies, for up to 16 weeks, confirmed ALC <500/mm^3 occurred in 0.3% of patients treated with 200 mg and 0% of patients treated with 100 mg or placebo. Both cases occurred in the first 4 weeks of exposure. Among all patients exposed to CIBINQO, including the long-term extension, confirmed ALC < 500/mm^3 were reported in 0.3% of patients treated with 200 mg and 0.1% of patients treated with 100 mg, all of whom were 65 years of age and older (see Section 4.4 Special warnings and precautions for use).

Lipid elevations

In placebo-controlled studies, for up to 16 weeks, there was a dose-related increase in low-density lipoprotein cholesterol (LDL-c), total cholesterol, and high-density lipoprotein cholesterol (HDL-c) relative to placebo at Week 4 which remained elevated through the final visit in the treatment period. There was no meaningful change in the LDL/HDL ratio in patients treated with abrocitinib relative to patients treated with placebo. Events related to hyperlipidaemia occurred in 0.4% of patients exposed to CIBINQO 100 mg, 0.6% of patients exposed to 200 mg and 0% of patients exposed to placebo (see Section 4.4 Special warnings and precautions for use).

Creatine phosphokinase elevations (CPK)

In placebo-controlled studies, for up to 16 weeks, significant increases in CPK values (> 5 × ULN) occurred in 1.8% of patients treated with placebo, 1.8% of patients treated with 100 mg

and 3.8% of patients treated with 200 mg of CIBINQO, respectively. Most elevations were transient, and none led to discontinuation.

Nausea

In placebo-controlled studies, for up to 16 weeks, nausea was reported in 1.8% of patients treated with placebo and in 6.3% and 15.1% of patients treated with 100 mg and 200 mg, respectively. Discontinuation due to nausea occurred in 0.4% of patients treated with CIBINQO. Among patients with nausea, 63.5% of patients had onset of nausea in the first week of CIBINQO therapy. The median duration of nausea was 15 days. Most of the cases were mild to moderate in severity.

Retinal Detachment

In the placebo-controlled trials, for up to 16 weeks, retinal detachment occurred in 1 subject (0.6 per 100 patient-years) treated with CIBINQO 100 mg. In all 5 clinical trials, including the long-term extension trial, retinal detachment occurred in 2 subjects (0.3 per 100 patient-years) treated with CIBINQO 100 mg.

Paediatric population

The pharmacokinetics, safety and efficacy of CIBINQO in paediatric patients have not yet been established.

CIBINQO has been studied in adolescents 12 to < 18 years of age. However, because of bone findings in juvenile rats (comparable to a 3 month-old human), additional long-term data in growing adolescents is needed to conclude that the benefits outweigh the risks.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

CIBINQO was administered in clinical studies up to a single oral dose of 800 mg. There is no experience with overdose of CIBINQO. There is no specific antidote for overdose with CIBINQO. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Treatment should be symptomatic and supportive.

Pharmacokinetic data up to and including a single oral dose of 800 mg in healthy adult volunteers indicate that more than 90% of the administered dose is expected to be eliminated within 48 hours.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatological preparations, agents for dermatitis, excluding corticosteroids, ATC code: D11AH08

Mechanism of action

Abrocitinib is a Janus kinase (JAK) 1 inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within signaling pathways, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Abrocitinib modulates the signaling pathway at the point of JAK1, preventing the phosphorylation and activation of STATs.

Abrocitinib reversibly and selectively inhibits JAK1 by blocking the adenosine triphosphate (ATP) binding site. In a cell-free isolated enzyme assay, abrocitinib has biochemical selectivity for JAK1 over the other 3 JAK isoforms JAK2 (28-fold), JAK3 (>340-fold) and tyrosine kinase (TYK) 2 (43-fold). In cellular settings, where JAK enzymes transmit signals in pairs (i.e., JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/JAK2, JAK2/TYK2), abrocitinib preferentially inhibits cytokine-induced STAT phosphorylation mediated by receptors utilising JAK1 relative to receptors utilising JAK2 only or JAK2/TYK2 pairs. The relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known. Both the parent compound and the active metabolites inhibit cytokine signalling with similar levels of selectivity.

Pharmacodynamic effects

Treatment with CIBINQO was associated with dose-dependent reduction in serum markers of inflammation, including high sensitivity C-reactive protein (hsCRP), interleukin-31 (IL-31) and thymus and activation-regulated chemokine (TARC). These changes returned to near baseline within 4 weeks of drug discontinuation.

Clinical efficacy and safety

The efficacy and safety of CIBINQO as monotherapy and in combination with background medicated topical therapies over 12-16 weeks were evaluated in 1,616 patients in 3 pivotal Phase 3 randomised, double-blind, placebo-controlled studies (MONO-1, MONO-2, and COMPARE). In addition, the efficacy and safety of CIBINQO in monotherapy over 52 weeks (with the option of rescue treatment in flaring subjects) was evaluated in 1,233 subjects in a Phase 3 induction, randomised withdrawal, double-blind, placebo-controlled study (REGIMEN). The patients in these 4 studies were 12 years of age and older with moderate-to-severe atopic dermatitis as defined by Investigator's Global Assessment (IGA) score ≥3, Eczema Area and Severity Index (EASI) score ≥16, BSA involvement ≥10%, and Peak Pruritus Numerical Rating Scale (PP-NRS) ³ 4 at baseline prior to randomisation. Patients who had a prior inadequate response or for whom topical treatments were medically unadvisable, or who had received systemic therapies were eligible for inclusion. All patients who completed the parent studies were eligible to enrol into the long-term extension study EXTEND.

Baseline characteristics

In the placebo-controlled studies (MONO-1, MONO-2, COMPARE) and the open-label induction, randomised withdrawal study (REGIMEN), across all treatment groups 41.4% to 51.1% were female, 59.3% to 77.8% were Caucasian, 15.0% to 33.0% were Asian and 4.1% to 8.3% were Black, and the mean age was 32.1 to 37.7 years. In these studies, 32.2% to 40.8% had a baseline IGA of 4 (severe atopic dermatitis), and 41.4% to 59.5% of patients had received prior systemic treatment for atopic dermatitis. The baseline mean EASI score ranged from 28.5 to 30.9, the baseline PP-NRS ranged from 7.0 to 7.3 and the baseline Dermatology Life Quality Index (DLQI) ranged from 14.4 to 16.0.

Clinical response

Treatment with CIBINQO 100 mg or 200 mg once daily as monotherapy or in combination with background medicated topical therapy resulted in improvement in objective signs of atopic dermatitis and patient-reported pruritus.

Monotherapy studies

In both pivotal monotherapy studies (MONO-1, MONO-2), the proportion of patients who achieved IGA and/or EASI-75 response was significantly higher in patients who received CIBINQO 100 mg or 200 mg once daily compared with placebo at Week 12 (see Table 6).

A significantly higher proportion of patients who achieved PP-NRS4 (defined as an improvement of ≥4 points in the severity PP-NRS) with CIBINQO 100 mg or 200 mg once daily compared with placebo was observed as soon as Week 2 and persisting through Week 12. Higher proportions of patients achieved PP-NRS4 with CIBINQO 100 mg or 200 mg once daily compared with placebo by Day 6 and Day 3 (2 days after the first dose), respectively.

Table 6. Efficacy results of CIBINQO monotherapy at Week 12

	MONO-1			MONO-2		
	ABR			ABR		
	200 mg QD N=154	100 mg QD N=156	Placebo N=77	200 mg QD N=155	100 mg QD N=158	Placebo N=78
	% Responders (95% CI)					
IGA 0 or 1[a]	43.8[g] (35.9, 51.7)	23.7[e] (17.0, 30.4)	7.9 (1.8, 14.0)	38.1[g] (30.4, 45.7)	28.4[f] (21.3, 35.5)	9.1 (2.7, 15.5)
EASI-50[b]	75.8[k] (69.0, 82.6)	57.7[k] (49.9, 65.4)	22.4 (13.0, 31.7)	79.9[k] (73.5, 86.2)	68.4[k] (61.1, 75.7)	19.5 (10.6, 28.3)
EASI-75[b]	62.7[g] (55.1, 70.4)	39.7[g] (32.1, 47.4)	11.8 (4.6, 19.1)	61.0g (53.3, 68.7)	44.5[g] (36.7, 52.3)	10.4 (3.6, 17.2)
EASI-90[b]	38.6[k] (30.8, 46.3)	18.6[i] (12.5, 24.7)	5.3 (0.2, 10.3)	37.7[k] (30.0, 45.3)	23.9[k] (17.2, 30.6)	3.9 (0.0, 8.2)
EASI-100[b]	13.1[i] (7.7, 18.4)	6.4[h] (2.6, 10.3)	0 (0.0, 4.7)	7.1[h] (3.1, 11.2)	5.2[h] (1.7, 8.6)	0 (0.0, 4.7)
PP-NRS4[c,d]	57.2[g] (48.8, 65.6)	37.7[f] (29.2, 46.3)	15.3 (6.6, 24.0)	55.3[g] (47.2, 63.5)	45.2[g] (37.1, 53.3)	11.5 (4.1, 19.0)
PP-NRS (0 or 1)	35.4[k] (27.2, 43.6)	21.1[i] (13.9, 28.4)	3.2 (0.0, 7.5)	32.4[k] (24.5, 40.2)	21.3[i] (14.5, 28.0)	5.5 (0.3, 10.7)

Table 6. Efficacy results of CIBINQO monotherapy at Week 12

	MONO-1			MONO-2		
	ABR			ABR		
	200 mg QD N=154	100 mg QD N=156	Placebo N=77	200 mg QD N=155	100 mg QD N=158	Placebo N=78
	% Change from baseline (95% CI)					
LSM EASI	-73.5[k] (-79.1, -68.0)	-57.5[k] (-63.1, -51.9)	-28.4 (-36.5, -20.3)	-73.3[k] (-79.7, -66.9)	-60.0[k] (-66.5, -53.6)	-28.6 (-38.4, -18.8)
LSM PP-NRS	-56.5[k] (-63.6, -49.5)	-39.5[i] (-46.7, -32.3)	-19.5 (-30.0, -9.0)	-56.9[k] (-64.0, -49.8)	-43.5[j] (-50.7, -36.3)	-20.8 (-31.6, -9.9)
LSM SCORAD	-55.1[k] (-60.1, -50.2)	-41.5[k] (-46.5, -36.5)	-21.6 (-28.7, -14.5)	-56.2[k] (-61.2, -51.1)	-45.8[k] (-50.9, -40.7)	-22.7 (-30.4, -15.1)
	Change from baseline (95% CI)					
LSM PSAAD	-3.2[g] (-3.6, -2.8)	-2.2[e] (-2.6, -1.9)	-1.1 (-1.7, -0.6)	-3.0[g] (-3.3, -2.7)	-2.4[g] (-2.8, -2.1)	-0.8 (-1.3, -0.3)

Abbreviations: ABR=abrocitinib; CI=confidence interval; EASI=Eczema Area and Severity Index; LSM=least squares mean; IGA=Investigator Global Assessment; N=number of patients randomised; PP-NRS=Peak Pruritus Numerical Rating Scale; PSAAD=Pruritus and Symptoms Assessment for Atopic Dermatitis; QD=once daily; SCORAD=SCORing Atopic Dermatitis.

a. IGA responders were patients with IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ³ 2 points.

b. EASI-50, -75, -90 and -100 responders were patients with ≥50%, ≥75%, ≥90%, and ≥100% improvement, respectively in EASI, from baseline.

c. The proportion of PP-NRS4 responders was also significantly higher with CIBINQO 200 mg and 100 mg once daily than placebo at Week 2, Week 4, and Week 8 in both MONO-1 and MONO-2.

d. PP-NRS4 responders were patients with ≥4-point improvement in PP-NRS from baseline.

e. Multiplicity-controlled p <0.01 versus placebo.

f. Multiplicity-controlled p <0.001 versus placebo.

g. Multiplicity-controlled p <0.0001 versus placebo.

h. Nominal p <0.05 versus placebo.

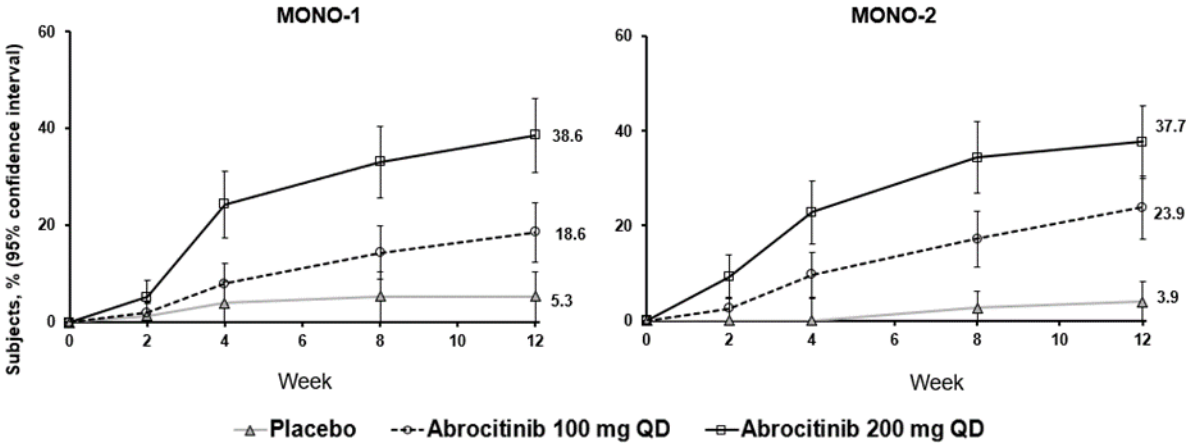
i. Nominal p <0.01 versus placebo.

j. Nominal p <0.001 versus placebo.

k. Nominal p <0.0001 versus placebo.

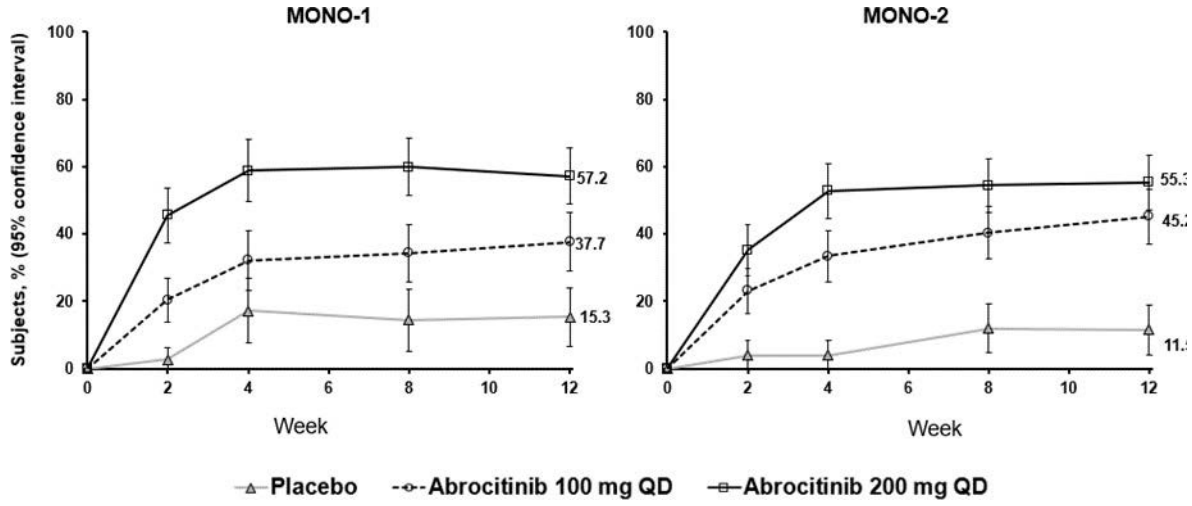
The proportion of patients who achieved EASI-90 or PP-NRS4 over time in studies MONO-1 and MONO-2 are shown in Figures 1 and 2.

Figure 1. Proportion of patients who achieved EASI-90 over time in MONO-1 and MONO-2



Abbreviations: EASI=Eczema Area and Severity Index; QD=once daily.
PP-NRS4 responders were patients with ≥4-point improvement in Peak Pruritis Numerical Rating Scale (PP-NRS) from baseline.

Figure 2. Proportion of patients who achieved PP-NRS4 over time in MONO-1 and MONO-2



Abbreviations: PP-NRS=Peak Pruritus Numerical Rating Scale; QD=once daily.
PP-NRS4 responders were patients with ≥4-point improvement in Peak Pruritis Numerical Rating Scale (PP-NRS) from baseline.

Treatment effects in subgroups (e.g., weight, age, sex, race and prior systemic immunosuppressant treatment) in MONO-1 and MONO-2 were consistent with the results in the overall study population.

Combination therapy study

In the pivotal combination therapy study (COMPARE), the proportion of patients who achieved IGA or EASI-75 response was significantly higher in patients who received CIBINQO 100 mg or 200 mg once daily compared with placebo at Week 12 (see Table 7).

The proportions of patients achieving PP-NRS4 with CIBINQO 100 mg and 200 mg once daily were significantly higher than placebo by Day 9 and Day 4, respectively, and remained significantly higher than placebo with both CIBINQO doses at Week 2 and Week 16.

The proportion of patients achieving PP-NRS4 with CIBINQO 200 mg once daily was significantly higher than dupilumab as early as Day 4 and remained significantly higher than dupilumab at Week 2. The proportion of patients achieving PP-NRS4 was similar between CIBINQO 100 mg once daily and dupilumab at Week 2.

Table 7. Efficacy results of CIBINQO with concomitant topical therapy

	Week 2				Week 12				Week 16			
	ABR				ABR				ABR			
	200 mg N=226	100 mg N=238	PBO N=131	DUP N=243	200 mg N=226	100 mg N=238	PBO N=131	DUP N=243	200 mg N=226	100 mg N=238	PBO N=131	DUP N=243
	% Responders											
IGA 0 or 1[a]	18.4[i]	15.2[h]	6.3	4.7	48.4[e]	36.6[e]	14.0	36.5	47.5[e]	34.8[e]	12.9	38.8
EASI-50[b]	60.5[j]	53.1[j]	21.9	35.7	86.3[j]	75.3[j]	52.7	80.9	87.3[j]	81.2[j]	57.3	84.1
EASI-75[b]	30.0[j]	25.4[i]	10.9	14.0	70.3[e]	58.7[e]	27.1	58.1	71.0[e]	60.3[e]	30.6	65.5
EASI-90[b]	11.2[h]	8.3[g]	2.3	2.6	46.1[j]	36.6[j]	10.1	34.9	48.9[j]	38.0[j]	11.3	38.8
EASI-100[b]	4.5[g]	1.3	0	0.4	12.3[i]	8.1[h]	1.6	6.6	13.6[h]	12.7[h]	4.0	5.2
PP-NRS4[c]	49.1[e,f]	31.8[d]	13.8	26.4	63.1[j]	47.5[i]	28.9	54.5	62.8[j]	47.0[h]	28.7	57.1
PP-NRS (0 or 1)	15.0[h]	8.9	4.6	4.6	36.9[j]	21.1[i]	7.4	24.9	32.0[i]	24.7[g]	11.7	24.2
	% Change from baseline											
LSM EASI	-54.6[j]	-49.3[j]	-21.2	-38.8	-80.6[j]	-73.8[j]	-47.7	-75.4	-83.2[j]	-75.2[j]	-53.8	-80.2
SM PP-NRS	-45.6[j]	-35.5[j]	-19.5	-29.3	-63.3[j]	-48.2[j]	-30.4	-54.8	-64.1[j]	-49.1[j]	-30.3	-58.5
LSM SCORAD	-41.7[j]	-34.6[j]	-18.1	-27.7	-65.2[j]	-54.2[j]	-33.5	-58.4	-65.4[j]	-55.6[j]	-38.8	-61.9
	Change from baseline											
LSM PSAAD	-2.3[j]	-1.8[j]	-0.9	-1.6	-3.6[j]	-2.7[j]	-1.6	-3.2	-3.6[j]	-2.8[j]	-1.7	-3.4

Abbreviations: ABR=abrocitinib; DUP=dupilumab; EASI=Eczema Area and Severity Index; LSM=least squares mean; N=number of patients randomised; PBO=placebo; PP-NRS=Peak Pruritus Numerical Rating Scale; PSAAD=Pruritus and Symptoms Assessment for Atopic Dermatitis; SCORAD=SCORing Atopic Dermatitis.

a. IGA responders were patients with IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ³ 2 points.

b. EASI-50, -75, -90 and -100 responders were patients with ≥50%, ≥75%, ≥90% and ≥100% improvement in EASI, respectively, from baseline.

c. PP-NRS4 responders were patients with ≥4-point improvement in PP-NRS from baseline.

d. Multiplicity-controlled p <0.001 vs. placebo

e. Multiplicity-controlled p <0.0001 vs. placebo

f. Multiplicity-controlled p <0.0001 vs. dupilumab. Statistical comparison between either abrocitinib dose and dupilumab was only performed on the proportion of patients achieving PP-NRS4 at Week 2.

g. Nominal p <0.05 vs. placebo

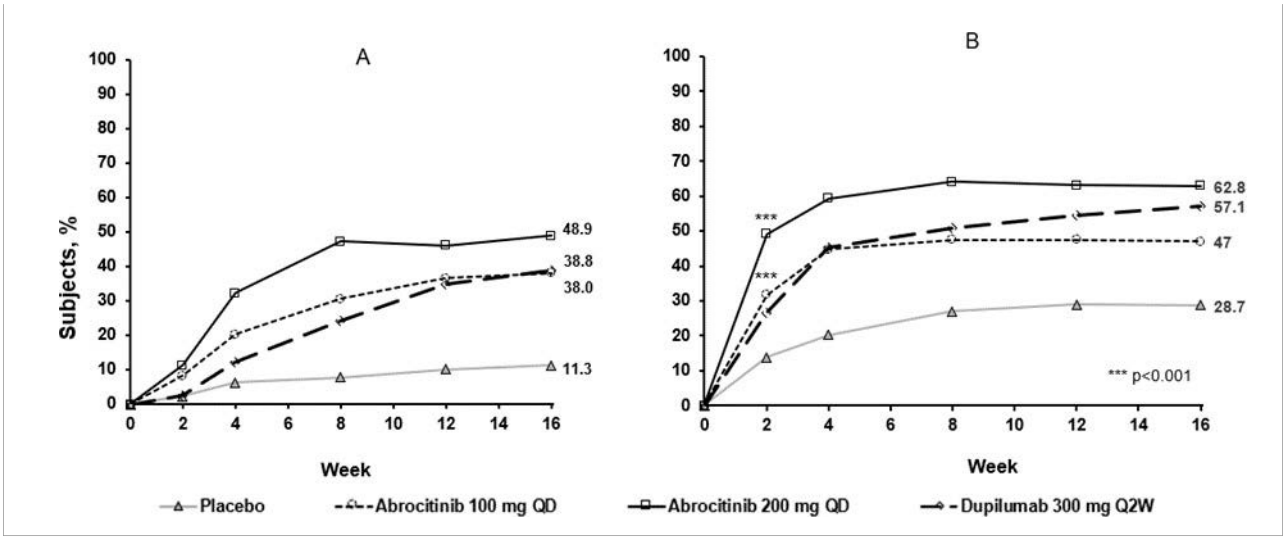
h. Nominal p <0.01 vs. placebo

i. Nominal p <0.001 vs. placebo

j. Nominal p <0.0001 vs. placebo

The proportion of patients who achieved EASI-90 or PP-NRS4 over time in COMPARE are shown in Figure 3.

Figure 3. Proportion of patients who achieved A) EASI-90 and B) PP-NRS4 over time in COMPARE



Abbreviations: EASI=Eczema Area and Severity Index; PP-NRS=Peak Pruritus Numerical Rating Scale; QD=once daily; Q2W=every 2 weeks.

EASI-90 was based on EASI ≥90% improvement from baseline.

PP-NRS4 response was based on achieving at least 4 points improvement in the severity of Peak Pruritus Numerical Rating Scale (PP-NRS).

*** p<0.001, statistically significant with adjustment for multiplicity vs placebo.

Patients who completed 16 weeks of dupilumab treatment and subsequently enrolled in EXTEND (N=203) were randomised to either CIBINQO 100 mg (N=130) or 200 mg once daily (N=73) upon entering EXTEND. Among responders to dupilumab in COMPARE, the majority maintained response 12 weeks after switching to CIBINQO [77% and 86% for IGA (0 or 1) response, 90% and 96% for EASI-75, and 82% and 92% for PP-NRS4 with 100 mg once daily and 200 mg once daily, respectively]. Among non-responders to dupilumab in COMPARE, a greater proportion of patients achieved response 12 weeks after switching to CIBINQO [34% and 47% for IGA (0 or 1) response, 68% and 80% for EASI-75, and 38% and 81% for PP-NRS4 with 100 mg once daily and 200 mg once daily, respectively]. There was no increase in adverse events in the subgroup of patients switching from dupilumab to CIBINQO, either those classified as responders or non-responders.

Treatment effects in subgroups (e.g., weight, age, sex, race, and prior systemic immunosuppressant treatment) in COMPARE were consistent with the results in the overall study population.

Open-label induction, randomised withdrawal study (REGIMEN)

A total of 1,233 patients received open-label CIBINQO. Seven-hundred ninety-eight (798) induction responders were randomised to 200 mg or 100 mg of medicinal product or placebo.

Continuous treatment (200 mg continuous) and induction-maintenance treatment (200 mg for 12 weeks followed by 100 mg) prevented flare with 81.1% and 57.4% probability, respectively,

vs 19.1% among patients who withdrew treatment (randomised to placebo) after 12 weeks of induction. Three-hundred fifty-one (351) patients including 16.2% of 200 mg, 39.2% of 100 mg and 76.4% of placebo patients received rescue medication of 200 mg CIBINQO in combination with topical therapy.

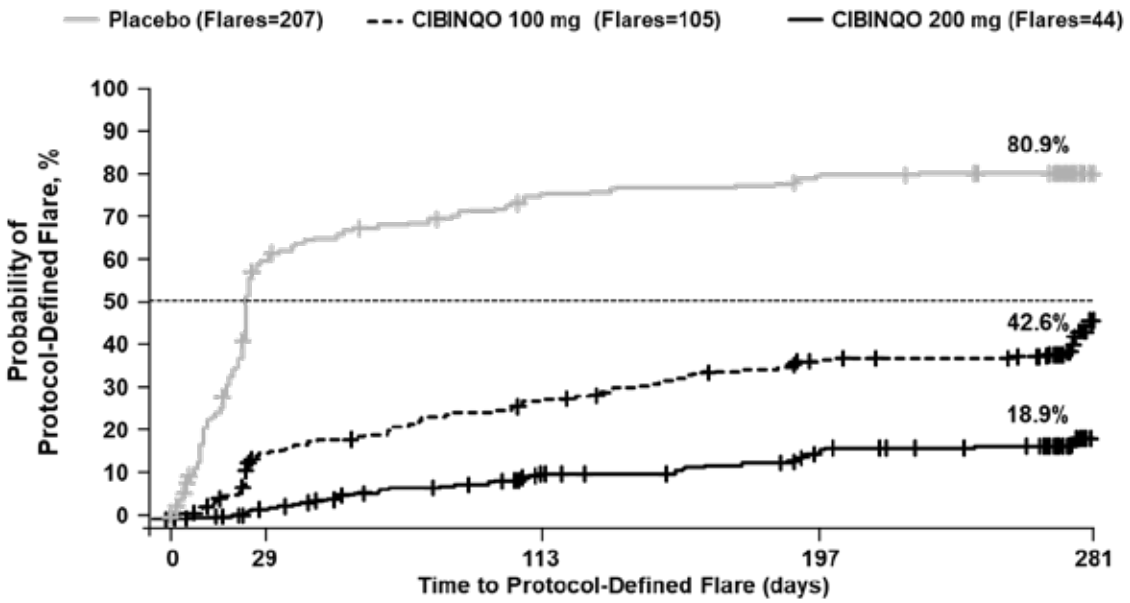
Table 8. Efficacy results of CIBINQO in REGIMEN

	CBQ monotherapy Open label induction, Week 12 200 mg N=1233
IGA 0 or 1[a] % responders (95% CI)	65.9 (63.3, 68.6)
EASI-75[b] % responders (95% CI)	75.6 (73.1, 78.0)
PP-NRS 4-point improvement[c] % responders (95% CI)	68.3 (65.3, 71.3)

Abbreviations: CBQ=CIBINQO; CI=confidence interval; EASI=Eczema Area and Severity Index; IGA=Investigator Global Assessment; N=number of patients randomised; PP-NRS=Peak Pruritus Numerical Rating Scale.

a. IGA responders were patients with IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ³ 2 points.
b. EASI-75 responders were patients with ≥ 75% improvement in EASI from baseline.
c. PP-NRS4 responders were patients with ≥ 4-point improvement in PP-NRS from baseline.

Figure 4. Time to protocol-defined flare



CIBINQO used in monotherapy
Protocol-defined flare=A loss of at least 50% of the EASI response at Week 12 and an IGA score of 2 or higher.
Multiplicity-controlled p < 0.0001 200 mg vs placebo; 100 mg vs placebo; 200 mg vs 100 mg.

A multivariate analysis was performed to identify predictors of successfully decreasing the dose from 200 mg to 100 mg and remaining flare-free for at least 12 weeks after the dose

decrease. In that analysis, patients who had not received prior systemic agents (HR 1.8, 95% CI 1.2, 2.6) and patients who had ≤ 50% BSA involvement before starting abrocitinib (HR 1.8, 95% CI 1.2, 2.6) were almost twice as likely to remain protocol-defined flare-free than those who had received prior systemic agents and who had > 50% BSA involvement.

In patients who discontinued CIBINQO treatment (randomised to placebo) after 12 weeks of induction, none met the criterion for worsening EASI score, and >97% had an EASI score less than or equal to their score at predose baseline through 40 weeks after discontinuing treatment. There were no adverse events related to rebound of atopic dermatitis.

Late-onset efficacy

Eligible patients who completed the full treatment period of a qualifying parent study (e.g., MONO-1, MONO-2, COMPARE) were considered for enrolment in the long-term extension study EXTEND, which allows patients to extend CIBINQO treatment for at least 92 weeks or until availability of commercial product in their country. In EXTEND, patients received CIBINQO with or without background medicated topical therapy. Patients who were previously randomised to CIBINQO 100 mg or 200 mg once daily in qualifying studies continued the same dose in EXTEND as in the parent study, and the blind was maintained. Patients not previously randomised to CIBINQO in a qualifying parent study were randomised to either CIBINQO 100 mg or 200 mg once daily upon entering EXTEND.

Among patients who did not achieve IGA (0 or 1) response after 12 weeks of CIBINQO treatment and entered EXTEND, 14% and 25% of patients continuing CIBINQO 100 mg once daily in EXTEND achieved IGA (0 or 1) response by Week 16 and Week 24 (with 4 and 12 additional weeks of treatment), respectively, and 19% and 29% of patients continuing CIBINQO 200 mg once daily achieved IGA response by Week 16 and Week 24, respectively (based on observed data) Among patients who did not achieve EASI-75 after 12 weeks of CIBINQO treatment and entered EXTEND, 32% and 50% of patients continuing CIBINQO 100 mg once daily in EXTEND achieved EASI-75 by Week 16 and Week 24 (with 4 and 12 additional weeks of treatment), respectively, and 33% and 57% of patients continuing CIBINQO 200 mg once daily achieved EASI-75 response by Week 16 and Week 24, respectively (based on observed data).

Long-term efficacy

Analysis of long-term efficacy was based on 595 patients receiving CIBINQO 100 mg and 521 patients receiving CIBINQO 200 mg once daily. Among these patients, 346 and 335 patients had received treatment for at least 96 weeks with 100 mg and 200 mg once daily, respectively. Among patients who achieved response at Week 12 of a qualifying parent study and entered EXTEND, the majority of patients maintained their response at Week 96 of cumulative CIBINQO treatment for both doses of CIBINQO [64% and 72% for IGA (0 or 1) response, 87% and 90% for EASI-75, and 75% and 80% for PP-NRS4 with 100 mg once daily and 200 mg once daily, respectively (based on observed data).

Health related outcomes

Treatment with either dose of CIBINQO as monotherapy resulted in greater improvement in patient-reported outcomes at 12 weeks compared with placebo (see Table 9). A larger proportion of the CIBINQO groups had clinically meaningful reductions in Dermatology Life Quality Index (DLQI) total scores (defined as a 4-point improvement) from baseline to Week 12 compared with placebo. CIBINQO groups also had a larger proportion of patients who

reported "no effect" of their disease on their quality of life (as measured by a DLQI score of 0 or 1).

Both groups improved patient-reported atopic dermatitis symptoms and sleep disruption as measured by the Patient Oriented Eczema Measure (POEM), Night Time Itch Scale (NTIS), and SCORing Atopic Dermatitis (SCORAD) sleep loss subscale. In addition, anxiety and depression symptoms as measured by the Hospital Anxiety and Depression Scale (HADS) total score had greater reduction in the CIBINQO groups compared with placebo at 12 weeks.

Table 9. Additional endpoint results with CIBINQO monotherapy at Week 12

	MONO-1			MONO-2		
	ABR			ABR		
	200 mg QD N=154	100 mg QD N=156	Placebo N=77	200 mg QD N=155	100 mg QD N=158	Placebo N=78
LSM SCORAD (sleep loss subscale)						
Baseline median (SD)	5.9	6.0	6.5	6.2	6.2	5.7
Change from baseline (95% CI)	-3.7[d] (-4.2, -3.3)	-2.9[c] (-3.4, -2.5)	-1.6 (-2.2, -1.0)	-3.8[d] (-4.2, -3.4)	-3.0[a] (-3.4, -2.6)	-2.1 (-2.7, -1.5)
NTIS >4-point improvement						
% responders	n/a	n/a	n/a	57.0[d]	42.7[d]	12.7
DLQI						
0 or 1, % responders	31.9[b]	20.2	12.1	26.6[c]	20.3[b]	5.7
≥4 point improvement, % responders	72.6[c]	67.2[b]	43.6	78.1[d]	73.3[d]	32.3
LSM DLQI						
Baseline mean (SD)	14.6 (6.8)	14.6 (6.5)	13.9 (7.3)	14.8 (6.0)	15.4 (7.3)	15.0 (7.1)
Change from baseline (95% CI)	-9.1[d] (-10.3, -8.0)	-7.0[b] (-8.1, -5.8)	-4.2 (-5.9, -2.5)	-9.8[d] (-10.7, -8.8)	-8.3[d] (-9.3, -7.3)	-3.9 (-5.3, -2.4)
CDLQI						
≥2.5 point improvement, % responders	83.9[a]	73.3	53.3	93..3[c]	56.3[a]	12.5
LSM-CDLQI						
Baseline mean (SD)	13.2 (5.5)	11.7 (6.6)	13.6 (7.0)	12.9 (5.7)	13.8 (5.8)	10.1 (3.8)
Change from baseline (95% CI)	-7.5[a] (-8.9, -6.0)	-6.4 (-7.9, -5.0)	-3.9 (-6.1, -1.7)	-9.7[b] (-12.1, -7.4)	-4.8 (-7.2, -2.5)	-2.7 (-6.1, 0.8)
LSM POEM						
Baseline mean (SD)	19.6 (5.9)	19.5 (6.5)	19.9 (6.1)	19.7 (5.7)	20.9 (5.7)	19.2 (5.5)
Change from baseline (95% CI)	-10.6[d] (-11.8, -9.4)	-6.8[b] (-8.0, -5.6)	-3.7 (-5.5, -1.9)	-11.0[d] (-12.1, -9.8)	-8.7[d] (-9.9, -7.5)	-3.6 (-5.3, -1.9)
LSM HADS (anxiety)						
Baseline mean (SD)	5.6 (4.0)	5.9 (4.1)	6.0 (4.0)	5.9 (3.9)	5.5 (4.2)	6.0 (3.7)
Change from baseline (95% CI)	-2.1[b] (-2.5, -1.6)	-1.6 (-2.0, -1.1)	-1.0 (-1.7, -0.4)	-1.7[a] (-2.2, -1.2)	-1.6[a] (-2.1, -1.1)	-0.6 (-1.3, 0.2)
LSM HADS (depression)						
Baseline mean (SD)	4.2 (3.7)	4.1 (3.7)	3.9 (3.5)	4.0 (3.7)	4.1 (4.0)	4.4 (3.3)
Change from baseline (95% CI)	-1.8[d] (-2.2, -1.4)	-1.4[b] (-1.8, -0.9)	-0.2 (-0.8, 0.4)	-1.4[d] (-1.8, -1.0)	-1.0[c] (-1.5, -0.6)	0.3 (-0.3, 0.9)

Abbreviations: ABR=abrocitinib; CDLQI=Child Dermatology Life Quality Index; CI=confidence interval; DLQI=Dermatology Life Quality Index; HADS=Hospital Anxiety and Depression Scale; LSM=least squares

mean; N=number of patients randomised; n/a= not available; NTIS=Night Time Itch Scale Severity; POEM=Patient Oriented Eczema Measure; QD=once daily; SCORAD=SCORing Atopic Dermatitis.
a. Nominal p <0.05 versus placebo.
b. Nominal p <0.01 versus placebo.
c. Nominal p <0.001 versus placebo.
d. Nominal p <0.0001 versus placebo.

In COMPARE, a larger proportion of the CIBINQO groups had clinically meaningful reductions in DLQI total scores (defined as a 4-point improvement) from baseline to Week 12 compared with placebo (see Table 10). CIBINQO groups also had a larger proportion of patients who reported "no effect" of their disease on their quality of life (as measured by a DLQI score of 0 or 1).

Both groups improved patient-reported atopic dermatitis symptoms and sleep disruption as measured by the POEM and SCORAD sleep loss subscale, respectively. In addition, anxiety and depression symptoms as measured by the HADS total score had a greater reduction in the CIBINQO groups compared with placebo at 12 weeks.

Table 10. Additional endpoint results with CIBINQO in combination with medicated topical therapies at Week 12

	COMPARE		
	ABR		
	200 mg QD + Topical N=226	**100 mg QD + Topical N=238**	**Placebo + Topical N=131**
LSM SCORAD (sleep loss subscale)			
Baseline mean values	6.4	6.1	6.0
Change from baseline	-4.6[d]	-3.7[d]	-2.4
(95% CI)	(-4.9, -4.3)	(-4.0, -3.4)	(-2.8, -2.0)
NTIS >4-point improvement			
% responders	64.3[d]	54.0[c]	34.4
DLQI			
0 or 1, % responders	29.7%[d]	21.9%[b]	8.6%
≥4 point improvement, % responders	86.4%[d]	74.7%[c]	56.5%
LSM DLQI			
Baseline mean (SD)	16.3 (6.6)	15.5 (6.4)	15.2 (6.9)
Change from baseline	-11.0[d]	-8.7[d]	-6.2
(95% CI)	(-11.7, -10.3)	(-9.4, -8.0)	(-7.1, -5.3)
LSM POEM			
Baseline mean (SD)	21.5 (5.3)	20.9 (5.5)	20.4 (6.1)
Change from baseline	-12.6[d]	-9.6[d]	-5.1
(95% CI)	(-13.6, -11.7)	(-10.5, -8.6)	(-6.3, -3.9)
LSM HADS (anxiety)			
Baseline mean (SD)	5.5 (3.8)	5.3 (3.9)	5.3 (3.9)
Change from baseline	-1.6[c]	-1.2[a]	-0.4
(95% CI)	(-2.0, -1.2)	(-1.5, -0.8)	(-0.9, 0.1)
LSM HADS (depression)			
Baseline mean (SD)	3.9 (3.4)	4.0 (3.3)	4.1 (3.7)
Change from baseline	-1.6[d]	-1.3[c]	-0.3
(95% CI)	(-1.9, -1.2)	(-1.6, -0.9)	(-0.7, 0.2)

Abbreviations: ABR=abrocitinib; DLQI=Dermatology Life Quality Index; HADS=Hospital Anxiety and Depression Scale; LSM=least squares mean; NTIS=Night Time Itch Scale Severity; POEM=Patient Oriented Eczema Measure; QD=once daily; SCORAD=SCORing Atopic Dermatitis; SD=standard deviation.

a. Nominal p <0.05 versus placebo.
b. Nominal p <0.01 versus placebo.
c. Nominal p <0.001 versus placebo.
d. Nominal p <0.0001 versus placebo.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of abrocitinib is characterised by rapid absorption (peak plasma concentrations are reached within 1 hour), and an elimination half-life of about 5 hours. Steady-state plasma concentrations of abrocitinib are achieved within 48 hours after once daily administration.

Absorption

Effect of Food

Abrocitinib is well-absorbed with over 91% extent of oral absorption and absolute oral bioavailability of approximately 60%. Both C_{max} and AUC of abrocitinib increased dose proportionally up to 400 mg. Coadministration of CIBINQO with a high-fat meal had no clinically relevant effect on abrocitinib exposures (AUC and C_{max} increased by approximately 26% and 29%, respectively, and T_{max} was prolonged by 2 hours). In clinical studies, CIBINQO was administered without regard to food (see Section 4.2 Dose and method of administration).

Distribution

After intravenous administration, the volume of distribution of abrocitinib is about 100 L. Approximately 64%, 37% and 29% of circulating abrocitinib and its active metabolites M1 and M2, respectively, are bound to plasma proteins. Abrocitinib and its active metabolites distribute equally between red blood cells and plasma.

Metabolism

The metabolism of abrocitinib is mediated by multiple CYP enzymes, CYP2C19 (~53%), CYP2C9 (~30%), CYP3A4 (~11%) and CYP2B6 (~6%). In a human radiolabelled study, abrocitinib was the most prevalent circulating species, with 3 polar mono-hydroxylated metabolites identified as M1 (3-hydroxypropyl), M2 (2-hydroxypropyl), and M4 (pyrrolidinone pyrimidine). Of the 3 metabolites in circulation, M1 and M2 have similar JAK inhibitory profiles as abrocitinib, while M4 was pharmacologically inactive. The pharmacological activity of CIBINQO is attributable to the unbound exposures of parent molecule as well as M1 and M2 in systemic circulation. The sum of unbound exposures of abrocitinib, M1 and M2, each expressed in molar units and adjusted for relative potencies, is referred to as the abrocitinib active moiety.

Elimination

Abrocitinib is eliminated primarily by metabolic clearance mechanisms, with less than 1% of the dose excreted in urine as unchanged drug. The metabolites of abrocitinib, M1, M2 and M4 are excreted predominantly in urine, and are substrates of OAT3 transporter.

Special populations

Body Weight, Gender, Genotype, Race, and Age

Body weight, gender, CYP2C19/2C9 genotype, race, and age did not have a clinically meaningful effect on CIBINQO exposure (see Section 4.2 Dose and method of administration).

Paediatric (under 12 years of age)

The pharmacokinetics of CIBINQO in paediatric patients under 12 years of age have not yet been established (see Section 4.2 Dose and method of administration).

Renal impairment

In a renal impairment study, patients with severe (eGFR <30 mL/min) and moderate (eGFR 30 to <60 mL/min) renal impairment had approximately 191% and 110% increase in active moiety AUC_{inf}, respectively, compared to patients with normal renal function (eGFR ≥90 mL/min; see Section 4.2 Dose and method of administration). Based on these results, a clinically significant increase in abrocitinib active moiety is not expected in patients with mild renal impairment (creatinine clearance 60 to <90 mL/min). The eGFR in individual patients was estimated using Modification of Diet in Renal Disease (MDRD) formula.

CIBINQO has not been studied in patients with ESRD on renal replacement therapy (see Section 4.2 Dose and method of administration). In Phase 3 clinical studies, CIBINQO was not evaluated in patients with atopic dermatitis with baseline creatinine clearance values less than 40 mL/min.

Hepatic impairment

Patients with mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment had approximately 4% decrease and 15% increase in active moiety AUC_{inf}, respectively, compared to patients with normal hepatic function. These changes are not clinically significant, and no dose adjustment is required in patients with mild or moderate hepatic impairment (see Section 4.2 Dose and method of administration). In clinical studies, CIBINQO was not evaluated in patients with severe (Child Pugh C) hepatic impairment (see Section 4.3 Contraindications), or in patients screened positive for active hepatitis B or hepatitis C (see Section 4.4 Special warnings and precautions for use).

5.3 Preclinical safety data

Genotoxicity

Abrocitinib was not mutagenic in the bacterial mutagenicity assay (Ames assay). Although abrocitinib was aneugenic in the in vitro TK6 micronucleus assay, abrocitinib was not aneugenic or clastogenic *in vivo* in the rat bone marrow micronucleus assay.

Carcinogenicity

No evidence of tumourigenicity was observed in Tg.rasH2 mice administered abrocitinibor 26 weeks at oral doses up to 75 mg/kg/day and 60 mg/kg/day in female and male mice, respectively. However, maximum tested exposures were subclinical. In a 104-week oral carcinogenicity study, a higher incidence of benign thymomas in female rats was seen at clinically-relevant exposures. No evidence of abrocitinib-related tumourigenicity was observed

following oral abrocitinib administration in male rats at exposures equal to 14 times the unbound human AUC at the MRHD of 200 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Calcium hydrogen phosphate
Sodium starch glycollate
Magnesium stearate

Film-coat
Hypromellose (E464)
Titanium dioxide (E171)
Lactose monohydrate
Macrogol 3350
Triacetin (E1518)
Iron red oxide (E172)

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Keep in original package. Store below 30 °C.

6.5 Nature and contents of container

CIBINQO 50mg, CIBINQO 100 mg and CIBINQO 200mg are available in Blister packs containing 7 film coated tablet Starter Packs and 28 film coated tablet Commercial Packs.

Each tablet is packed in a unit dose polyvinylidene chloride (PVDC) blister with an aluminium foil lidding.

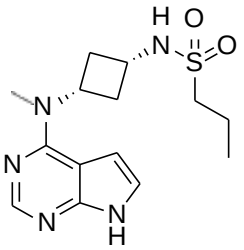
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



CAS number

1622902-68-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Medicine)

8. SPONSOR

Pfizer Australia Pty Ltd
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Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

DD Month YYYY

10. DATE OF REVISION

Not applicable

Summary Table of Changes

Section changed	Summary of new information
N/A	N/A