

Cibinqo LPD CC 030123

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cibinqo 50 mg
Cibinqo 100 mg
Cibinqo 200 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cibinqo 50 mg

Each film-coated tablet contains 50 mg of abrocitinib.

Excipient with known effect

Each film-coated tablet contains 1.37 mg of lactose monohydrate.

Cibinqo 100 mg film-coated tablets

Each film-coated tablet contains 100 mg of abrocitinib.

Excipient with known effect

Each film-coated tablet contains 2.73 mg of lactose monohydrate.

Cibinqo 200 mg film-coated tablets

Each film-coated tablet contains 200 mg of abrocitinib.

Excipient with known effect

Each film-coated tablet contains 5.46 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Cibinqo 50 mg film-coated tablets

Oval pink film-coated tablet debossed with "PFE" on one side and "ABR 50" on the other.

Cibinqo 100 mg film-coated tablets

Round pink film-coated tablet debossed with "PFE" on one side and "ABR 100" on the other.

Cibinqo 200 mg film-coated tablets

Oval pink film-coated tablet debossed with "PFE" on one side and "ABR 200" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

2022-0082833

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Cibinqo is indicated for the treatment of moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a healthcare professional experienced in the diagnosis and treatment of atopic dermatitis.

Posology

The recommended starting dose is 200 mg once daily.

- A starting dose of 100 mg once daily is recommended for patients ≥ 65 years of age and in patients at high risk for DVT/PE. For other patients who may benefit from a starting dose of 100 mg, see sections 4.4 and 4.8.
- During treatment, the dose may be decreased or increased based on tolerability and efficacy. The lowest effective dose for maintenance should be considered. The maximum daily dose is 200 mg.

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

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

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 $< 50 \times 10^3/\text{mm}^3$.
		ALC: Treatment should be interrupted if ALC is $< 0.5 \times 10^3/\text{mm}^3$ and may be restarted once ALC returns above this value. Treatment should be discontinued if confirmed.
		ANC: Treatment should be interrupted if ANC is $< 1 \times 10^3/\text{mm}^3$ 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 should not be initiated in patients with a platelet count $< 150 \times 10^3/\text{mm}^3$, an absolute lymphocyte count (ALC) $< 0.5 \times 10^3/\text{mm}^3$, an absolute neutrophil count (ANC) $< 1.2 \times 10^3/\text{mm}^3$ or who have a haemoglobin value < 10 g/dL (see section 4.4).

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Dose interruption

If a patient develops a serious infection, sepsis or opportunistic infection, dose interruption should be considered until the infection is controlled (see section 4.4).

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, dosing should be resumed at the regular scheduled time.

Interactions

In patients receiving dual strong inhibitors of CYP2C19 and moderate inhibitors of CYP2C9, or strong inhibitors of CYP2C19 alone (e.g. fluvoxamine, fluconazole, fluoxetine and ticlopidine), the recommended dose should be reduced by half to 100 mg or 50 mg once daily (see section 4.5).

Treatment is not recommended concomitantly with moderate or strong inducers of CYP2C19/CYP2C9 enzymes (e.g. rifampicin, apalutamide, efavirenz, enzalutamide, phenytoin) (see section 4.5).

In patients receiving acid reducing agents (e.g. antacids, proton pump inhibitors and H2 receptor antagonists), 200 mg once daily dose of abrocitinib should be considered (see section 4.5).

Special populations

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.

Abrocitinib has not been studied in patients with eGFR < 40 mL/min. The recommended dose is based on extrapolation.

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In patients with moderate (eGFR 30 to < 60 mL/min) renal impairment, the recommended dose of abrocitinib should be reduced by half to 100 mg or 50 mg once daily (see section 5.2).

In patients with severe (eGFR < 30 mL/min) renal impairment, 50 mg once daily is the recommended starting dose. The maximum daily dose is 100 mg (see section 5.2).

Abrocitinib has not been studied in patients with end-stage renal disease (ESRD) on renal replacement therapy.

Hepatic impairment

No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Abrocitinib is contraindicated to patients with severe (Child Pugh C) hepatic impairment (see section 4.3).

Elderly

The recommended starting dose for patients aged 65 years or more is 100 mg once daily (see section 4.4).

Paediatric population

The safety and efficacy of Cibinqo in children under 12 years of age have not yet been established. No data are available.

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) (see section 5.3), additional long-term data in growing adolescents is needed to conclude that the benefits outweigh the risks. Currently available data are described in sections 4.8, 5.1 and 5.2.

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Method of administration

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

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

Tablets should be swallowed whole with water and should not be split, crushed or chewed because these methods have not been studied in clinical trials.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active serious systemic infections, including tuberculosis (TB) (see section 4.4).
- Severe hepatic impairment (see section 4.2).
- Pregnancy and breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Serious infections

Serious infections have been reported in patients receiving abrocitinib. The most frequent serious infections in clinical studies were herpes simplex, herpes zoster and pneumonia (see section 4.8).

Treatment must not be initiated in patients with an active, serious systemic infection (see section 4.3).

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

- with chronic or recurrent infection
- who have been exposed to TB
- 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 abrocitinib. A patient who develops a new infection during treatment should undergo prompt and complete diagnostic testing and appropriate antimicrobial therapy should be initiated. The patient should be closely monitored and therapy should be temporarily interrupted if the patient is not responding to standard therapy.

Tuberculosis

Tuberculosis was observed in clinical studies with abrocitinib. Patients should be screened for TB before starting treatment and yearly screening for patients in highly endemic areas for TB should be considered. Abrocitinib must not be given to patients with active TB (see section 4.3). 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 treatment.

Viral reactivation

Viral reactivation, including herpes virus reactivation (e.g. herpes zoster, herpes simplex), was reported in clinical studies. The rate of herpes zoster infections was higher in patients who were treated with 200 mg, 65 years of age and older, with a medical history of herpes zoster, with a confirmed ALC $< 1 \times 10^3/\text{mm}^3$ prior to the event and patients with severe atopic dermatitis at baseline (see section 4.8). If a patient develops herpes zoster, temporary interruption of treatment should be considered until the episode resolves.

Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy and during therapy. Patients with evidence of active hepatitis B or hepatitis C (positive hepatitis C PCR) infection were excluded from clinical studies (see section 5.2). 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

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DNA negative or below LLQ could initiate treatment; 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 abrocitinib. Use of live, attenuated vaccines should be avoided during or immediately prior to treatment. Prior to initiating treatment with this medicinal product, it is recommended that patients be brought up to date with all immunisations, including prophylactic herpes zoster vaccinations, in agreement with current immunisation guidelines.

Thrombotic events including pulmonary embolism

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving abrocitinib (see section 4.8). Abrocitinib should be used with caution in patients at high risk for DVT/PE. Risk 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. If clinical features of DVT/PE occur, treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.

Malignancy (including non-melanoma skin cancers)

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

The risks and benefits of abrocitinib treatment should be considered prior to initiating in patients with a known malignancy other than a successfully treated NMSC or cervical cancer *in situ* or when considering continuing therapy in patients who develop a malignancy. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Haematologic abnormalities

Confirmed ALC $< 0.5 \times 10^3/\text{mm}^3$ and platelet count $< 50 \times 10^3/\text{mm}^3$ were observed in less than 0.5% of patients in clinical studies (see section 4.8). Treatment with abrocitinib should not be initiated in patients with a platelet count $< 150 \times 10^3/\text{mm}^3$, an ALC $< 0.5 \times 10^3/\text{mm}^3$, an ANC $< 1.2 \times 10^3/\text{mm}^3$ or who have a haemoglobin value $< 10 \text{ g/dL}$ (see section 4.2). Complete blood count should be monitored 4 weeks after initiation of therapy and thereafter according to routine patient management (see Table 1).

Lipids

Dose-dependent increases in blood lipid parameters were reported in patients treated with abrocitinib compared to placebo (see section 4.8). Lipid parameters should be assessed approximately 4 weeks following initiation of therapy and thereafter according to the patient's risk for cardiovascular disease (see Table 1). 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 abrocitinib compared to that of other available therapies for atopic dermatitis should be considered. If abrocitinib is chosen, interventions to manage lipid concentrations should be implemented according to clinical guidelines.

Elderly

The safety profile observed in elderly patients was similar to that of the adult population with the following exceptions: a higher proportion of patients 65 years of age and older discontinued from clinical studies and were more likely to have serious adverse reactions compared to younger patients; patients 65 years and older were more likely to

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

Immunosuppressive conditions or medicinal products

Patients with immunodeficiency disorders or a first-degree relative with a hereditary immunodeficiency were excluded from clinical studies and no information on these patients is available.

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.

Excipients

Lactose monohydrate

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicines to affect pharmacokinetics of abrocitinib

Abrocitinib is metabolised predominantly by CYP2C19 and CYP2C9 enzymes, and to a lesser extent by CYP3A4 and CYP2B6 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 inhibit or induce these enzymes and transporter. Dose adjustments, as appropriate, are outlined in section 4.2.

Co-administration with CYP2C19/CYP2C9 inhibitors

When 100 mg abrocitinib 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 (see section 5.2) increased by 91% and 155%, respectively, compared with administration alone (see section 4.2).

Co-administration with CYP2C19/CYP2C9 inducers

Administration of 200 mg abrocitinib after multiple doses with rifampicin, a strong inducer of CYP enzymes, resulted in reduction of abrocitinib active moiety exposures by approximately 56% (see section 4.2).

Co-administration with OAT3 inhibitors

When abrocitinib 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.

Co-administration with products which increase gastric pH

When abrocitinib 200 mg was administered concomitantly with famotidine 40 mg, an H₂-receptor antagonist, abrocitinib active moiety exposures decreased by approximately 35%. The effect of elevating gastric pH with antacids, or proton pump inhibitors (omeprazole) on the pharmacokinetics of abrocitinib has not been studied and may be

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similar to that seen with famotidine. The higher 200 mg daily dose should be considered for patients treated concomitantly with products which increase gastric pH, as they may reduce the efficacy of abrocitinib.

Potential for abrocitinib to affect pharmacokinetics of other medicinal products

No clinically significant effects of abrocitinib were observed in interaction studies with oral contraceptives (e.g. ethinyl oestradiol/levonorgestrel).

In vitro, abrocitinib is an inhibitor of P glycoprotein (P-gp). Co-administration of dabigatran etexilate (a P-gp substrate), with a single dose of abrocitinib 200 mg increased dabigatran AUC_{inf} and C_{max} by approximately 53% and 40%, respectively, compared with administration alone. Caution should be exercised for concomitant use of abrocitinib with dabigatran. The effect of abrocitinib on the pharmacokinetics of other P-gp substrates has not been evaluated. Caution should be exercised as the levels of P-gp substrates with a narrow therapeutic index, such as digoxin, may increase.

In vitro, abrocitinib is an inhibitor of CYP2C19 enzyme. Co-administration of abrocitinib 200 mg once daily with omeprazole 10 mg single dose increased the AUC_{inf} and C_{max} of omeprazole by approximately 189% and 134%, respectively, indicating that abrocitinib is a moderate inhibitor of CYP2C19 enzyme. Caution should be exercised when using abrocitinib concomitantly with narrow therapeutic index medicines that are primarily metabolised by CYP2C19 enzyme (e.g. S-mephenytoin and clopidogrel). Dose adjustment may be required for other medicines primarily metabolised by CYP2C19 enzyme in accordance with their product information (e.g. citalopram, clobazam, escitalopram and selumetinib).

Co-administration of abrocitinib 200 mg once daily with caffeine 100 mg single dose increased the AUC_{inf} of caffeine by 40% with lack of effect on C_{max}, suggesting that abrocitinib is a mild inhibitor of CYP1A2 enzyme. No general dose adjustment can be recommended.

4.6 Fertility, pregnancy and lactation

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.

Pregnancy

There are no or limited amount of data on the use of abrocitinib in pregnant women. Studies in animals have shown reproductive toxicity. Abrocitinib has been shown to cause embryo-foetal lethality in pregnant rats and rabbits, skeletal variations in the fetuses of pregnant rats and rabbits, and to affect parturition and peri/postnatal development in rats (see section 5.3). Cibinqo is contraindicated during pregnancy (see section 4.3).

Breast-feeding

There are no data on the presence of abrocitinib in human milk, the effects on the breast-fed 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 breast-feeding (see section 4.3).

Fertility

Based on the findings in rats, oral administration of Cibinqo may result in temporary reduced fertility in females of reproductive potential. The effects on female rat fertility were reversible 1 month after cessation of abrocitinib oral administration (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions 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).

Tabulated list of adverse reactions

A total of 3 582 patients were treated with abrocitinib in clinical studies in atopic dermatitis. Among them 2 784 patients (representing 3 006 patient-years of exposure) were treated with consistent dosing regimens of either abrocitinib 100 mg (1 023 patients) or 200 mg (1 761 patients). There were 1 451 patients with at least 48 weeks of exposure. 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 abrocitinib in comparison to placebo for up to 16 weeks.

Listed in Table 2 are adverse reactions observed in atopic dermatitis clinical studies presented by system organ class and frequency, using the following categories: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1 000$ to $< 1/100$); rare ($\geq 1/10 000$ to $< 1/1 000$); very rare ($< 1/10 000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2. Adverse reactions

System organ class	Very common	Common	Uncommon
Infections and infestations		Herpes simplex ^a Herpes zoster ^b	Pneumonia
Blood and lymphatic system disorders			Thrombocytopenia Lymphopenia
Metabolism and nutrition disorders			Hyperlipidaemia ^c
Nervous system disorders		Headache Dizziness	
Vascular disorders			Thrombotic events including pulmonary embolism ^d
Gastrointestinal disorders	Nausea	Vomiting Abdominal pain upper	
Skin and subcutaneous tissue disorders		Acne	
Investigations		Creatine phosphokinase increased $> 5 \times \text{ULN}^e$	

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. 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 abrocitinib 100 mg and 200 mg, respectively. Most infections were mild or moderate. The percentage of patients reporting infection-related adverse reactions in the 200 mg and

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100 mg groups compared to placebo were: herpes simplex (4.2% and 2.8% versus 1.4%), herpes zoster (1.2% and 0.6% versus 0%), pneumonia (0.1% and 0.1% versus 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. Most opportunistic infections were cases of herpes zoster (0.61 per 100 patient-years in the abrocitinib 100 mg group and 1.23 per 100 patient-years in the abrocitinib 200 mg group), most of which were non-serious multidermatomal cutaneous infections. Among all patients treated in clinical studies with consistent dosing regimens of either abrocitinib 100 mg or 200 mg, including the long-term extension study, the incidence rate of herpes zoster in patients treated with abrocitinib 200 mg (4.83 per 100 patient-years) was higher than that of patients treated with 100 mg (2.39 per 100 patient-years). Incidence rates for herpes zoster were also higher for patients 65 years of age and older (HR 3.68), patients with a medical history of herpes zoster (HR 3.61), patients with severe atopic dermatitis at baseline (HR 1.28), and a confirmed ALC $< 1.0 \times 10^3/\text{mm}^3$ prior to the event of herpes zoster (HR 1.84) (see section 4.4).

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 in clinical studies with consistent dosing regimens of either abrocitinib 100 mg or 200 mg, including the long-term extension study, the rate of serious infections was 2.43 per 100 patient-years treated with 100 mg and 2.46 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).

Thrombotic events including pulmonary embolism

Among all patients treated in clinical studies with consistent dosing regimens of either abrocitinib 100 mg or 200 mg, including the long-term extension study, the rate of PE was 0.17 per 100 patient-years for 200 mg and 0.08 per 100 patient-years for 100 mg. The rate of DVT was 0.11 per 100 patient-years in the 200 mg group and 0 per 100 patient-years in the 100 mg group (see section 4.4).

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 $< 50 \times 10^3/\text{mm}^3$ were reported in 0.1% of patients exposed to 200 mg, and in 0 patients treated with 100 mg or placebo. Among all patients treated with clinical studies with consistent dosing regimens of either abrocitinib 100 mg or 200 mg, including the long-term extension study, the rate of confirmed platelet counts of $< 50 \times 10^3/\text{mm}^3$ was 0.17 per 100 patient-years for 200 mg and 0 per 100 patient-years for 100 mg, most occurring at Week 4. Patients 65 years of age and older had a higher rate of platelet counts $< 75 \times 10^3/\text{mm}^3$ (see section 4.4).

Lymphopenia

In placebo-controlled studies, for up to 16 weeks, confirmed ALC $< 0.5 \times 10^3/\text{mm}^3$ 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 treated in clinical studies with consistent dosing regimens of either abrocitinib 100 mg or 200 mg, including the long-term extension, the rate of confirmed ALC $< 0.5 \times 10^3/\text{mm}^3$ was 0.56 per 100 patient-years for 200 mg and 0 per 100 patient-years for 100 mg, the highest rate was observed in patients 65 years of age and older (see section 4.4).

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 abrocitinib 100 mg, 0.6% of patients exposed to 200 mg and 0% of patients exposed to placebo (see section 4.4).

Creatine phosphokinase elevations (CPK)

In placebo-controlled studies, for up to 16 weeks, significant increases in CPK values ($> 5 \times \text{ULN}$) 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 abrocitinib, respectively. Most elevations were transient and none led to discontinuation.

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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 abrocitinib. Among patients with nausea, 63.5% of patients had onset of nausea in the first week of therapy. The median duration of nausea was 15 days. Most of the cases were mild to moderate in severity.

Paediatric population

A total of 635 adolescent patients (12 to less than 18 years of age) were treated with abrocitinib in clinical studies in atopic dermatitis representing 851.5 patient-years of exposure. The safety profile observed in adolescents in atopic dermatitis clinical studies was similar to that of the adult population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il/>

4.9 Overdose

Cibinqo was administered in clinical studies up to a single oral dose of 800 mg and 400 mg daily for 28 days. Adverse reactions were comparable to those seen at lower doses and no specific toxicities were identified. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions (see section 4.8). Treatment should be symptomatic and supportive. There is no specific antidote for overdose with this medicinal product.

Pharmacokinetics 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.

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 haematopoiesis and immune cell function. JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Inhibition of JAK1 modulates the signalling pathways by preventing the phosphorylation and activation of STATs.

In biochemical assays, abrocitinib has selectivity for JAK1 over the other 3 JAK isoforms JAK2 (28-fold), JAK3 (> 340-fold) and tyrosine kinase 2 (TYK2, 43-fold). In cellular settings, it preferentially inhibits cytokine-induced STAT phosphorylation by signalling pairs involving JAK1, and spares signalling by JAK2/JAK2, or JAK2/TYK2 pairs. The relevance of selective enzymatic inhibition of specific JAK enzymes to clinical effect is not currently known.

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Pharmacodynamic effects

Clinical biomarkers

Treatment with abrocitinib was associated with dose-dependent reduction in serum biomarkers of inflammation in atopic dermatitis [interleukin-31 (IL-31), interleukin-22 (IL-22), eosinophil count, and thymus and activation-regulated chemokine (TARC)], JAK1 signalling [natural killer (NK) cell count and interferon gamma-induced protein 10 (IP-10)] or both [high sensitivity C-reactive protein (hsCRP)]. These changes were reversible after treatment discontinuation.

Mean absolute lymphocyte count increased by 2 weeks after starting treatment with abrocitinib and returned to baseline by Month 9 of treatment. Most patients maintained an ALC within the reference range. Treatment with abrocitinib was associated with a dose-related increase in B cell counts and a dose-related decrease in NK cell counts. The clinical significance of these changes in B cell and NK cell counts is unknown.

Cardiac electrophysiology

The effect of abrocitinib on the QTc interval was examined in subjects who received a single supratherapeutic dose of abrocitinib 600 mg in a placebo- and positive-controlled thorough QT study. A concentration-dependent QTc prolonging effect of abrocitinib was seen; the mean (90% confidence interval) for the increase in QTc interval was 6.0 (4.52, 7.49) msec, indicating the lack of a clinically relevant effect of abrocitinib on QTc interval at the dose tested.

Clinical efficacy and safety

The efficacy and safety of abrocitinib 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 abrocitinib in monotherapy over 52 weeks (with the option of rescue treatment in flaring patients) was evaluated in 1 233 patients 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 $\geq 10\%$, and Peak Pruritus Numerical Rating Scale (PP-NRS) ≥ 4 at baseline prior to randomisation. Patients who had a prior inadequate response or for whom topical treatments were medically inadvisable, 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. A total of 134 patients 65 years of age and older were enrolled in these studies. 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

12-week monotherapy (MONO-1, MONO-2) and 16-week combination therapy (COMPARE) studies

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A significantly larger proportion of patients achieved both primary endpoints IGA 0 or 1 and/or EASI-75 with 100 mg or 200 mg once daily abrocitinib compared with placebo at Week 12 or Week 16 (see Table 3 and Table 4).

A significantly greater proportion of patients achieved at least a PP-NRS 4-point improvement with 100 mg or 200 mg once daily abrocitinib compared with placebo. This improvement was observed as early as Week 2 and persisted through Week 12 (Figure 1).

In the COMPARE study, superiority of abrocitinib 200 mg compared with dupilumab at Week 2 was demonstrated for the proportion of patients achieving at least a PP-NRS 4-point improvement with significantly higher itch responses seen as early as Day 4 after the first dose.

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

Table 3. Efficacy results of abrocitinib in monotherapy at Week 12

	MONO-1 ^d			MONO-2 ^d		
	Week 12			Week 12		
	Abrocitinib monotherapy		PBO N=77	Abrocitinib monotherapy		PBO N=78
200 mg QD N=154	100 mg QD N=156	200 mg QD N=155		100 mg QD N=158		
	% Responders (95% CI)					
IGA 0 or 1 ^a	43.8 ^e (35.9, 51.7)	23.7 ^e (17.0, 30.4)	7.9 (1.8, 14.0)	38.1 ^e (30.4, 45.7)	28.4 ^e (21.3, 35.5)	9.1 (2.7, 15.5)
EASI-75 ^b	62.7 ^e (55.1, 70.4)	39.7 ^e (32.1, 47.4)	11.8 (4.6, 19.1)	61.0 ^e (53.3, 68.7)	44.5 ^e (36.7, 52.3)	10.4 (3.6, 17.2)
PP-NRS4 ^c	57.2 ^e (48.8, 65.6)	37.7 ^e (29.2, 46.3)	15.3 (6.6, 24.0)	55.3 ^e (47.2, 63.5)	45.2 ^e (37.1, 53.3)	11.5 (4.1, 19.0)

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

- 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 ≥ 2 points.
- EASI-75 responders were patients with $\geq 75\%$ improvement in EASI from baseline.
- PP-NRS4 responders were patients with ≥ 4 -point improvement in PP-NRS from baseline.
- Abrocitinib used as monotherapy.
- Statistically significant with adjustment for multiplicity versus placebo.

Table 4. Efficacy results of abrocitinib in combination with topical therapy at Week 12 and Week 16

	COMPARE ^d							
	Week 12			Week 16				
	Abrocitinib + topicals		PBO + topicals N=131	DUP + topicals N=243	Abrocitinib + topicals		PBO + topicals N=131	DUP + topicals N=243
200 mg QD N=226	100 mg QD N=238	200 mg QD N=226			100 mg QD N=238			
	% Responders (95% CI)							
IGA 0 or 1 ^a	48.4 ^e (41.8, 55.0)	36.6 ^e (30.4, 42.8)	14.0 (8.0, 19.9)	36.5 (30.4, 42.6)	47.5 ^e (40.9, 54.1)	34.8 ^e (28.6, 40.9)	12.9 (7.0, 18.8)	38.8 (32.5, 45.1)
EASI-75 ^b	70.3 ^e (64.3, 76.4)	58.7 ^e (52.4, 65.0)	27.1 (19.5, 34.8)	58.1 (51.9, 64.3)	71.0 ^e (65.1, 77.0)	60.3 ^e (53.9, 66.6)	30.6 (22.5, 38.8)	65.5 (59.4, 71.6)
PP-NRS4 ^c	63.1 (56.7, 69.6)	47.5 (40.9, 54.1)	28.9 (20.8, 37.0)	54.5 (47.9, 61.0)	62.8 (55.6, 70.0)	47.0 (39.5, 54.6)	28.7 (19.6, 37.9)	57.1 (50.1, 64.2)

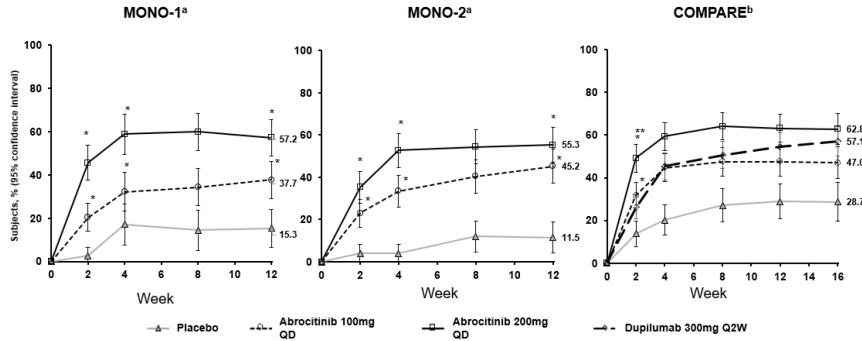
Abbreviations: CI=confidence interval; DUP=Dupilumab; EASI=Eczema Area and Severity Index; IGA=Investigator Global Assessment; N=number of patients randomised; PBO=placebo; PP-NRS=Peak Pruritus Numerical Rating Scale; QD=once daily.

- 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 ≥ 2 points.
- EASI-75 responders were patients with $\geq 75\%$ improvement in EASI from baseline.
- PP-NRS4 responders were patients with ≥ 4 -point improvement in PP-NRS from baseline.
- Abrocitinib used in combination with topical therapy.
- Statistically significant with adjustment for multiplicity versus placebo.

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The proportion of patients who achieved PP-NRS4 over time in studies MONO-1, MONO-2 and COMPARE are shown in Figure 1.

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



Abbreviations: PP-NRS=Peak Pruritus Numerical Rating Scale; QD=once daily; Q2W=every 2 weeks. PP-NRS4 responders were patients with ≥ 4 -point improvement in PP-NRS from baseline.

a. Abrocitinib used as monotherapy.

b. Abrocitinib used in combination with medicated topical therapy.

* Statistically significant with adjustment for multiplicity versus placebo.

** Statistically significant with adjustment for multiplicity versus dupilumab.

Health-related outcomes

In both monotherapy studies (MONO-1 and MONO-2) and in the combination therapy study (COMPARE), abrocitinib significantly improved patient-reported outcomes, including itch, sleep (SCORAD Sleep VAS), AD symptoms (POEM), quality of life (DLQI) and symptoms of anxiety and depression (HADS) that were uncorrected for multiplicity, at 12 weeks compared to placebo (see Table 5).

Table 5. Patient-reported outcomes results of abrocitinib monotherapy and in combination with topical therapy at Week 12

	Monotherapy						Combination therapy		
	MONO-1			MONO-2			COMPARE		
	200 mg QD	100 mg QD	PBO	200 mg QD	100 mg QD	PBO	200 mg QD + topicals	100 mg QD + topicals	PBO + topicals
N	154	156	77	155	158	78	226	238	131
SCORAD Sleep VAS, change from baseline (95% CI)	-3.7* (-4.2, -3.3)	-2.9* (-3.4, -2.5)	-1.6 (-2.2, -1.0)	-3.8* (-4.2, -3.4)	-3.0* (-3.4, -2.6)	-2.1 (-2.7, -1.5)	-4.6* (-4.9, -4.3)	-3.7* (-4.0, -3.4)	-2.4 (-2.8, -2.0)
DLQI ≥ 4 -point improvement, % responders	72.6%*	67.2%*	43.6%	78.1%*	73.3%*	32.3%	86.4%*	74.7%*	56.5%
POEM, change from baseline (95% CI)	-10.6* (-11.8, -9.4)	-6.8* (-8.0, -5.6)	-3.7 (-5.5, -1.9)	-11.0* (-12.1, -9.8)	-8.7* (-9.9, -7.5)	-3.6 (-5.3, -1.9)	-12.6* (-13.6, -11.7)	-9.6* (-10.5, -8.6)	-5.1 (-6.3, -3.9)
HADS Anxiety, change from baseline (95% CI)	-2.1* (-2.5, -1.6)	-1.6 (-2.0, -1.1)	-1.0 (-1.7, -0.4)	-1.7* (-2.2, -1.2)	-1.6* (-2.1, -1.1)	-0.6 (-1.3, 0.2)	-1.6* (-2.0, -1.2)	-1.2* (-1.5, -0.8)	-0.4 (-0.9, 0.1)
HADS Depression, change from baseline (95% CI)	-1.8* (-2.2, -1.4)	-1.4* (-1.8, -0.9)	-0.2 (-0.8, 0.4)	-1.4* (-1.8, -1.0)	-1.0* (-1.5, -0.6)	0.3 (-0.3, 0.9)	-1.6* (-1.9, -1.2)	-1.3* (-1.6, -0.9)	-0.3 (-0.7, 0.2)

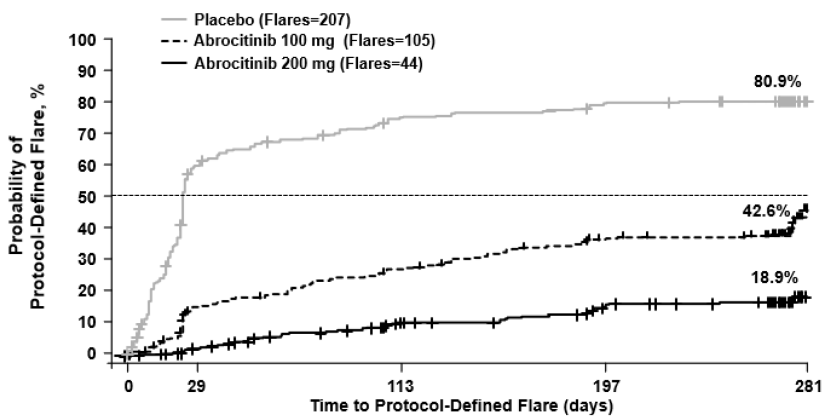
CI=confidence interval; DLQI=Dermatology Life Quality Index; HADS=Hospital Anxiety and Depression Scale; N=number of patients randomised; PBO=placebo; POEM=Patient-Oriented Eczema Measure; QD=once daily; SCORAD=SCORing for AD; VAS=visual analog scale.

Open-label induction, randomised withdrawal study (REGIMEN)

A total of 1 233 patients received open-label abrocitinib 200 mg once daily in the 12-week run-in phase. Among these patients, 798 patients (64.7%) met responder criteria (defined as achieving IGA [0 or 1] response and EASI-75) and were randomised to placebo (267 patients), abrocitinib 100 mg once daily (265 patients) or abrocitinib 200 mg once daily (266 patients).

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, versus 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 abrocitinib in combination with topical therapy.

Figure 2. Time to protocol-defined flare



Abrocitinib used as 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 versus placebo; 100 mg versus placebo; 200 mg versus 100 mg.

Long-term efficacy

Eligible patients who completed the full treatment period of a qualifying parent study (e.g. MONO-1, MONO-2, COMPARE, REGIMEN) were considered for enrolment in the long-term extension study EXTEND. In EXTEND, patients received abrocitinib with or without background medicated topical therapy. Patients who were previously randomised to medicinal product 100 mg or 200 mg once daily in parent studies continued the same dose in EXTEND as in the parent study. In EXTEND, patients received double-blind treatment until the parent study was completed, after which patients received single-blind treatment (treatment assignment disclosed to the investigators but not to the patients).

Among patients who achieved response after 12 weeks of treatment and entered EXTEND, the majority of patients maintained their response at Week 48 of cumulative treatment for both doses of abrocitinib [60% and 70% for IGA (0 or 1) response, 79% and 87% for EASI-75, and 62% and 83% for PP-NRS4 with 100 mg once daily and 200 mg once daily, respectively].

Among patients who did not achieve response after 12 weeks of treatment and entered EXTEND, a proportion of patients achieved late-onset response by Week 24 (from baseline) of continued treatment with abrocitinib [25% and 29% for IGA (0 or 1) response, and 50% and 59% for EASI-75 with 100 mg once daily and 200 mg once daily,

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respectively]. Patients who achieved partial response at Week 12 were more likely than those with no response at Week 12 to achieve treatment benefit at Week 24.

Patients who received dupilumab in the COMPARE study and subsequently entered EXTEND were randomised to either 100 mg or 200 mg of abrocitinib once daily upon entering EXTEND. Among non-responders to dupilumab, a substantial proportion of patients achieved response 12 weeks after switching to abrocitinib [34% and 47% for IGA (0 or 1) response, and 68% and 80% for EASI-75 with 100 mg once daily or 200 mg once daily, respectively].

Paediatric population

The efficacy and safety of abrocitinib as monotherapy was evaluated in 2 Phase 3 randomised, double-blind, placebo-controlled studies (MONO-1, MONO-2) which included 124 patients who were 12 to less than 18 years of age. The efficacy and safety were also evaluated in an open-label induction, randomised withdrawal study (REGIMEN), which included 246 patients who were 12 to less than 18 years of age. In these studies, the results in the adolescent subgroup were consistent with the results in the overall study population.

The efficacy and safety of abrocitinib in combination with background medicated topical therapy were evaluated in the Phase 3 randomised, double-blind, placebo-controlled study TEEN. The study included 287 patients who were 12 to less than 18 years of age with moderate-to-severe atopic dermatitis as defined by IGA score ≥ 3 , EASI score ≥ 16 , BSA involvement $\geq 10\%$, and PP-NRS ≥ 4 at the baseline visit prior to randomisation. Patients who had a prior inadequate response or who had received systemic therapy, were eligible for inclusion.

Baseline characteristics

In TEEN, across all treatment groups 49.1% were female, 56.1% were Caucasian, 33.0% were Asian and 6.0% were Black patients. The median age was 15 years and the proportion of patients with severe atopic dermatitis (IGA of 4) was 38.6%.

Table 6. Adolescent efficacy results in TEEN

	TEEN ^d		
	Abrocitinib		PBO
	200 mg QD N=96	100 mg QD N=95	N=96
IGA 0 or 1 ^a	46.2 ^c	41.6 ^c	24.5
% responders (95% CI)	(36.1, 56.4)	(31.3, 51.8)	(15.8, 33.2)
EASI-75 ^b	72.0 ^c	68.5 ^c	41.5
% responders (95% CI)	(62.9, 81.2)	(58.9, 78.2)	(31.5, 51.4)
PP-NRS4 ^c	55.4 ^c	52.6	29.8
% responders (95% CI)	(44.1, 66.7)	(41.4, 63.9)	(20.0, 39.5)

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

- 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 ≥ 2 points.
- EASI-75 responders were patients with $\geq 75\%$ improvement in EASI from baseline.
- PP-NRS4 responders were patients with ≥ 4 -point improvement in PP-NRS from baseline.
- Abrocitinib used in combination with medicated topical therapy.
- Statistically significant with adjustment for multiplicity versus placebo.

5.2 Pharmacokinetic properties

Absorption

Abrocitinib is well-absorbed with over 91% extent of oral absorption and absolute oral bioavailability of approximately 60%. The oral absorption of abrocitinib is rapid and peak plasma concentrations are reached within 1 hour. Steady-state plasma concentrations of abrocitinib are achieved within 48 hours after once daily administration. Both C_{max} and AUC of abrocitinib increased dose proportionally up to 200 mg. Co-administration of abrocitinib with a high-fat meal had no clinically relevant effect on abrocitinib exposures (AUC and C_{max} increased by approximately

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26% and 29%, respectively, and T_{max} was prolonged by 2 hours). In clinical studies, abrocitinib was administered without regard to food (see section 4.2).

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.

Biotransformation

The *in vitro* 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 mainly 3 polar mono-hydroxylated metabolites identified as M1 (3-hydroxypropyl), M2 (2-hydroxypropyl) and M4 (pyrrolidinone pyrimidine). At steady state, M2 and M4 are major metabolites and M1 is a minor metabolite. Of the 3 metabolites in circulation, M1 and M2 have similar JAK inhibitory profiles as abrocitinib, while M4 was pharmacologically inactive. The pharmacologic activity of abrocitinib is attributable to the unbound exposures of parent molecule (~60%) as well as M1 (~10%) and M2 (~30%) 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.

No clinically significant effects of abrocitinib were observed in interaction studies with substrates of BCRP and OAT3 (e.g. rosuvastatin), MATE1/2K (e.g. metformin), CYP3A4 (e.g. midazolam), and CYP2B6 (e.g. efavirenz).

Elimination

The elimination half-life of abrocitinib is about 5 hours. Abrocitinib is eliminated primarily by metabolic clearance mechanisms, with less than 1% of the dose excreted in urine as unchanged active substance. 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 abrocitinib exposure (see section 4.2).

Adolescents (≥ 12 to <18 years)

Based on population pharmacokinetic analysis, there was no clinically relevant difference in mean abrocitinib steady-state exposures in adolescent patients compared to adults at their typical body weights.

Paediatric (< 12 years)

Interaction studies have been performed in adults only. The pharmacokinetics of abrocitinib in children under 12 years of age have not yet been established (see section 4.2).

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). Pharmacokinetics of abrocitinib have not been determined in patients with mild renal impairment, however, based on the results observed in other groups, an increase of up to 70% in active moiety exposure is expected in patients with mild renal impairment (eGFR 60 to < 90 mL/min). The increase of up to 70% is not clinically meaningful as the efficacy and safety of abrocitinib in atopic dermatitis

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patients with mild renal impairment (n=756) was comparable to the overall population in Phase 2 and 3 clinical studies. The eGFR in individual patients was estimated using Modification of Diet in Renal Disease (MDRD) formula.

Abrocitinib has not been studied in patients with ESRD on renal replacement therapy (see section 4.2). In Phase 3 clinical studies, abrocitinib 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). In clinical studies, abrocitinib was not evaluated in patients with severe (Child Pugh C) hepatic impairment (see section 4.3), or in patients screened positive for active hepatitis B or hepatitis C (see section 4.4).

5.3 Preclinical safety data

General toxicity

Decreased lymphocyte counts and decreased size and/or lymphoid cellularity of organs/tissues of the immune and haematopoietic systems were observed in nonclinical studies and were attributed to the pharmacological properties (JAK inhibition) of abrocitinib.

In toxicity studies of up to 1 month of abrocitinib dosing in rats at an age comparable to adolescent human age of ≥ 12 years, a microscopic bone dystrophy finding, considered transient and reversible, was noted, and exposure margins at which no bone finding was noted were 5.7 to 6.1 times the human AUC at the maximum recommended human dose (MRHD) of 200 mg. No bone findings were observed in rats at any dose in the 6-month toxicity study (up to 25 times the human AUC at the MRHD of 200 mg) or in any of the toxicity studies in cynomolgus monkeys (comparable to human age of ≥ 8 years; up to 30 times the human AUC at the MRHD of 200 mg).

Genotoxicity

Abrocitinib was not mutagenic in the bacterial mutagenicity assay (Ames assay). It was not aneugenic or clastogenic based on the results of the *in vivo* rat bone marrow micronucleus assay.

Carcinogenicity

No evidence of tumorigenicity was observed in the 6-month Tg.rasH2 mice administered abrocitinib at oral doses up to 75 mg/kg/day and 60 mg/kg/day in female and male mice, respectively. In the 2-year carcinogenicity study, higher incidence of benign thymoma was noted in female rats at the lowest dose tested. Thus, a lowest observed adverse effect level (LOAEL) is set in females at exposures equal to 0.6 times the human AUC at the MRHD of 200 mg. In males the no observed adverse effect level (NOAEL) was set at exposures equal to 13 times the human AUC at the MRHD of 200 mg. The human relevance of benign thymoma is unknown.

Reproductive and developmental toxicity

Abrocitinib had no effects on male fertility or spermatogenesis. Abrocitinib resulted in effects on female fertility (lower fertility index, corpora lutea, implantation sites and post-implantation loss), but no fertility effects were noted at exposures equal to 1.9 times the human AUC at the MRHD of 200 mg. The effects reversed 1 month after cessation of treatment.

No foetal malformations were observed in embryo-foetal development studies in rats or rabbits. In an embryo-foetal development study in pregnant rabbits, effects on embryo-foetal survival were noted at the lowest dose tested with exposures equal to 0.14 times the unbound human AUC at the MRHD of 200 mg. Increased litter incidences of

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unossified hindlimb phalanges and tarsals and forelimb phalanges were observed with effects on forelimb phalanges noted at exposures equal to 0.14 times the unbound human AUC at the MRHD of 200 mg.

In an embryo-foetal development study in pregnant rats, while increased embryo-foetal lethality was noted, none was observed at exposures equal to 10 times the human AUC at the MRHD of 200 mg. Increased incidence of skeletal variations of short 13th ribs, reduced ventral processes, thickened ribs, and unossified metatarsals were noted in the foetuses, but none were observed at exposures equal to 2.3 times the human AUC at the MRHD of 200 mg.

In a pre- and postnatal development study in pregnant rats, dams had dystocia with prolonged parturition, offspring had lower body weights and lower postnatal survival. No maternal or developmental toxicity was observed in either dams or offspring at exposures equal to 2.3 times the human AUC at the MRHD of 200 mg.

Administration of abrocitinib to juvenile rats (comparable to a 3 month old human) resulted in macroscopic and microscopic bone findings. When dosing was initiated at postnatal Day 10 (at exposures \geq 0.8 times the human AUC at the MRHD of 200 mg), macroscopic bone findings (malrotated and/or impaired use of forelimbs or hindlimbs or paws, fractures, and/or femoral head abnormalities) were noted. Only the microscopic bone dystrophy finding (similar to that observed in rat general toxicity studies of up to 1 month) was fully reversible after cessation of treatment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Dibasic calcium phosphate anhydrous
Sodium starch glycolate
Magnesium stearate

Film-coat (Opadry II Pink)

Hypromellose
Titanium dioxide
Lactose monohydrate
Macrogol
Triacetin
Iron oxide red

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf life after first opening

HDPE bottle: 45 days

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

2022-0082833

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Cibinqo 50 mg film-coated tablets

High-density polyethylene (HDPE) bottle and polypropylene closure containing 14 or 30 film-coated tablets.

Polyvinylidene chloride (PVDC) blister with aluminium foil lidding film containing 7 film-coated tablets. Each pack contains 14, 28 or 91 film-coated tablets.

Cibinqo 100 mg film-coated tablets

HDPE bottle and polypropylene closure containing 14 or 30 film-coated tablets.

PVDC blister with aluminium foil lidding film containing 7 film-coated tablets. Each pack contains 14, 28 or 91 film-coated tablets.

Cibinqo 200 mg film-coated tablets

HDPE bottle and polypropylene closure containing 14 or 30 film-coated tablets.

PVDC blister with aluminium foil lidding film containing 7 film-coated tablets. Each pack contains 14, 28 or 91 film-coated tablets.

Not all pack sizes may be marketed.

7. MARKETING AUTHORISATION HOLDER

Pfizer Pharmaceuticals Israel Ltd
9 Shenkar St Herzliya Pituach, 46725
Israel

Approved on 03/01/2023

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