Cibinqo

Abrocitinib

50 mg, 100 mg and 200 mg film-coated tablets

Reference market: UK

AfME markets using this LPD: Egypt

SUMMARY OF PRODUCT CHARACTERISTICS

Egypt, December 2024

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Cibinqo 50 mg film-coated tablets
Cibinqo 100 mg film-coated tablets
Cibinqo 200 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cibinqo 50 mg film-coated tablets
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
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 and adolescents 12 years and older 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 of Cibinqo is 100 mg or 200 mg once daily based on individual patient characteristics:

- A starting dose of 100 mg once daily is recommended for adolescents (12 to 17 years old), and for patients at higher risk of venous thromboembolism (VTE), major adverse cardiovascular event (MACE) and malignancy (see section 4.4). If the patient does not respond adequately to 100 mg once daily, the dose can be increased to 200 mg once daily (see below).
- A dose of 200 mg once daily may be appropriate for patients who are not at higher risk of VTE, MACE and malignancy with high disease burden 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.

Treatment initiation
Treatment should not be initiated in patients with a platelet count < $150 \times 10^3/mm^3$, an absolute lymphocyte count (ALC) < $0.5 \times 10^3/mm^3$, an absolute neutrophil count (ANC) < $1 \times 10^3/mm^3$ or who have a haemoglobin value < 8 g/dL (see section 4.4).

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 (see section 4.4).

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 strong inhibitors of cytochrome P450 (CYP) 2C19 (e.g. fluvoxamine, fluconazole, fluoxetine and ticlopidine), the recommended starting dose of Cibinqo should be reduced by half to 100 mg or 50 mg once daily.

The use of Cibinqo is not recommended concomitantly with moderate or strong inducers of CYP2C19/CYP2C9 enzymes (e.g. rifampicin, apalutamide, efavirenz, enzalutamide, phenytoin) (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.

In patients with moderate (eGFR 30 to < 60 mL/min) renal impairment, the recommended dose of Cibinqo 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).

Cibinqo 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. Cibinqo must not be used in patients with severe (Child Pugh C) hepatic impairment (see section 4.3).

Elderly
For patients 65 years of age and older, the recommended dose is 100 mg once daily (also see section 4.4).

Paediatric population
The recommended starting dose for adolescents (12 to 17 years old) is 100 mg once daily.

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

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 Cibinqo 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

Abrocitinib should only be used if no suitable treatment alternatives are available in patients: -65 years of age and older; -patients with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers); - patients with malignancy risk factors (e.g. current malignancy or a history of malignancy)

Infections/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).

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. In patients 65 years of age and older abrocitinib should only be used if no suitable treatment alternatives are available (see section 4.2).

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 Cibinqo 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 Cibinqo 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 Cibinqo.

Viral reactivation
Viral reactivation, including herpes virus reactivation (e.g. herpes zoster, herpes simplex), was reported in clinical studies (see section 4.8). 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 $<1\times10^3/mm^3$ 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.

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.

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). 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; 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 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.

Venous thromboembolism (VTE)

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving abrocitinib (see section 4.8).

In a large randomised active-controlled 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.

A higher rate of VTE was observed with abrocitinib 200 mg compared to abrocitinib 100 mg.

In patients with cardiovascular or malignancy risk factors (see also section 4.4 “Major adverse cardiovascular events (MACE)” and “Malignancy”) abrocitinib should only be used if no suitable treatment alternatives are available.

In patients with known VTE risk factors other than cardiovascular or malignancy risk factors, abrocitinib should be used with caution. VTE risk factors other than cardiovascular or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder.

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

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

Major adverse cardiovascular events (MACE)

Events of MACE have been observed in patients taking abrocitinib.

In a large randomised active-controlled 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.

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

Malignancy (excluding non-melanoma skin cancer [NMSC])

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

In a large randomised active controlled 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.

A higher rate of malignancies (excluding non-melanoma skin cancer, NMSC) was observed with abrocitinib 200 mg compared to abrocitinib 100 mg.

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 a history of malignancy), abrocitinib should only be used if no suitable treatment alternatives are available.

Non-melanoma skin cancer

NMSCs have been reported in patients receiving abrocitinib. Periodic skin examination is recommended for all patients, particularly those who are at increased risk for skin cancer.

Haematologic abnormalities

Confirmed ALC < $0.5 \times 10^3/mm^3$ and platelet count < $50 \times 10^3/mm^3$ were observed in less than 0.5% of patients in clinical studies (see section 4.8). Treatment with Cibinqo should not be initiated in patients with a platelet count < $150 \times 10^3/mm^3$, an ALC < $0.5 \times 10^3/mm^3$, an ANC < $1 \times 10^3/mm^3$ or who have a haemoglobin value < 8 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 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.

Laboratory monitoring

Table 1. Laboratory measure and monitoring guidance

Laboratory measure	Monitoring guidance	Action
	Before treatment initiation, 4 weeks after initiation and thereafter according to routine patient management.	Platelets: Treatment should be discontinued if platelet counts are < $50 \times 10^3/mm^3$.
		ALC: Treatment should be interrupted if ALC is

Complete blood count including Platelet Count, Absolute Lymphocyte Count (ALC), Absolute Neutrophil Count (ANC), and Haemoglobin (Hb)		$< 0.5 \times 10^3/mm^3$ and may be restarted once ALC returns above this value. Treatment should be discontinued if confirmed.
		ANC: Treatment should be interrupted if ANC is $< 1 \times 10^3/mm^3$ and may be restarted once ANC returns above this value.
		Hb: Treatment should be interrupted if Hb < 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 clinical guidelines for hyperlipidaemia.	Patients should be monitored according to clinical guidelines for hyperlipidaemia.

Elderly
A total of 176 patients 65 years of age and older were enrolled in Cibinqo studies. 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 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). There are limited data in patients above 75 years of age.

Use in patients 65 years of age and older

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

Excipients

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

Sodium content
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 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.

Co-administration with CYP2C19/CYP2C9 inhibitors

When 100 mg Cibinqo 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 Cibinqo 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). Based on the results of PBPK analysis, moderate induction of CYP enzymes reduces the exposure of abrocitinib active moiety by 44%.

Co-administration 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.

Co-administration with MAO inhibitors

In-vitro, abrocitinib showed reversible inhibition of MAO-A. Co administration of Cibinqo with MAO inhibitors such as selegiline or isocarboxazid, has not been studied in humans. Caution should be exercised for concomitant use of abrocitinib with MAO inhibitors.
Co-administration with products which increase gastric pH

The effect of elevating gastric pH on abrocitinib active moiety exposures is not clinically significant and dose adjustment is not needed.

When abrocitinib 200 mg was administered concomitantly with famotidine 40 mg, an H2-receptor antagonist, the peak and extent of abrocitinib active moiety exposures decreased by approximately 82% and 20% respectively. The effect of elevating gastric pH with antacids, or proton pump inhibitors (omeprazole) on the pharmacokinetics of abrocitinib has not been studied and may reduce the absorption of abrocitinib in a manner similar to that seen with famotidine.

Potential for Cibinqo to affect pharmacokinetics of other medicinal products

No clinically significant effects of Cibinqo were observed in drug interaction studies with oral contraceptives (e.g. ethinyl oestradiol/levonorgestrel), or with substrates of BCRP and OAT3 (e.g. rosuvastatin), MATE1/2K (e.g. metformin), CYP3A4 (e.g. midazolam), CYP1A2 (e.g. caffeine) and CYP2B6 (e.g. efavirenz).

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 Cibinqo 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 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 and ciclosporin, 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, clopidogrel).

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 skeletal variations in the foetuses 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

Cibinqo has no or negligible sedating effect. However, patients who experience dizziness after the intake of abrocitinib should refrain from driving or using machines until the dizziness resolves.

4.8 Undesirable effects

Summary of the safety profile

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).

Tabulated list of adverse reactions

A total of 3802 patients were treated with Cibinqo in clinical studies in atopic dermatitis, among them 3004 patients (representing 3680 patient-years of exposure) were integrated for safety analysis, 1549 with at least 48 weeks of exposure. The integrated safety analysis included 1981 patients receiving a constant dose of abrocitinib 200 mg and 1023 patients receiving a constant dose of 100 mg. 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.

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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 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			Venous thromboembolism[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 thromboembolism includes pulmonary embolism and 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% 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.

Among all patients treated in clinical studies with consistent dosing regimens of either Cibinqo 100 mg or 200 mg, including the long-term extension study, the incidence rate of herpes zoster in patients treated with abrocitinib 200 mg (4.70 per 100 patient-years) was higher than that of patients treated with 100 mg (2.11 per 100 patient-years). Incidence rates for herpes zoster were also higher for patients 65 years of age and older (HR 3.83), patients with a medical history of herpes zoster (HR 3.53), patients with severe atopic dermatitis at baseline (HR 1.16), and a confirmed ALC < 1.0 × $10^3/mm^3$ prior to the event of herpes zoster (HR 2.04) (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 Cibinqo 100 mg or 200 mg, including the long-term extension study, the rate of serious infections was 2.20 per 100 patient-years treated with 100 mg and 2.69 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).

Venous thromboembolism
Among all patients treated in clinical studies with consistent dosing regimen of either Cibinqo 100 mg or 200 mg, including the long-term extension study, the rate of PE was 0.06 per 100 patient-years for 100 mg group and 0.13 per 100 patient-years in the Cibinqo 200 mg group. The rate of DVT was 0.13 per 100 patient-years in the Cibinqo 100 mg group and 0.09 per 100 patient-years in the Cibinqo 200 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 $< 50 \times 10^3/mm^3$ were reported in 0.1% of patients treated with 200 mg, and in 0 patients treated with 100 mg or placebo. Among all patients treated in clinical studies with consistent dosing regimens of either Cibinqo 100 mg or 200 mg, including the long-term extension study, the rate of confirmed platelet counts of $<50 \times 10^3/mm^3$ was 0.22 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 $<75 \times 10^3/mm^3$ (see section 4.4).

Lymphopenia
In placebo-controlled studies, for up to 16 weeks, confirmed ALC $<0.5 \times 10^3/mm^3$ 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 Cibinqo 100 mg or 200 mg, including the long-term extension, the rate of confirmed ALC $<0.5 \times 10^3/mm^3$ was 0.40 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). There were no adolescent patients who developed an ALC $<0.5 \times 10^3/mm^3$.

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. The median % change in LDL-c at Week 4 was 9.1%, 4.9% and -2.8% in patients exposed to 200 mg, 100 mg and placebo, respectively; at Month 12 the median % change was 22.8% and 13.7% in the 200 mg and 100 mg groups, respectively. The median % change in HDL-c at Week 4 was 20.0%, 12.1%, and 0% in patients exposed to 200 mg. 100 mg and placebo, respectively; at Month 12 the median % change was 17.1% and 8.9% in the 200 mg and 100 mg groups, respectively. 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).

Creatine phosphokinase elevations (CPK)
In placebo-controlled studies, for up to 16 weeks, significant increases in CPK values ($> 5 \times$ 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. 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 therapy. The median duration of nausea was 15 days. Most of the cases were mild to moderate in severity.

Acne
In placebo-controlled studies, for up to 16 weeks, acne was reported in 0.2% of patients treated with placebo and in 1.8% and 4.8% of patients treated with 100 mg and 200 mg, respectively. No subjects discontinued due to an event of acne. All events were mild to moderate in severity.

Paediatric population

A total of 635 adolescents (12 to less than 18 years of age) were enrolled in Cibinqo atopic dermatitis studies 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 (see section 4.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after marketing authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

To report any side effect(s):

Egypt: Pharmacovigilance center, Pfizer Pharmaceutical Company: EGY.AEReporting@pfizer.com Egyptian Pharmacovigilance center (EPVC), EDA: pv.followup@edaegypt.gov.eg

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.

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

Cibinqo 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.

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 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 ≥ 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 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

12-week monotherapy (MONO-1, MONO-2) and 16-week TCS combination (COMPARE) studies
A significantly larger proportion of patients achieved both primary or key secondary endpoints IGA 0 or 1 and/or EASI-75 with 100 mg or 200 mg once daily Cibinqo 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 Cibinqo compared with placebo. Improvement was observed as early as Week 2 and persisting through Week 12 (Figure 1).

In the COMPARE study, superiority of Cibinqo 200 mg compared with dupilumab at Week 2 was demonstrated for the proportion of patients achieving 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 Cibinqo in monotherapy at Week 12

	MONO-1[c]			MONO-2[c]		
	Week 12			Week 12		
	CBQ monotherapy			CBQ monotherapy		
	200 mg QD N=154	100 mg QD N=156	PBO N=77	200 mg QD N=155	100 mg QD N=158	PBO N=78
	% Responders (95% CI)					
IGA 0 or 1[a]	43.8[d] (35.9, 51.7)	23.7[d] (17.0, 30.4)	7.9 (1.8, 14.0)	38.1[d] (30.4, 45.7)	28.4[d] (21.3, 35.5)	9.1 (2.7, 15.5)
EASI-75[b]	62.7[d] (55.1, 70.4)	39.7[d] (32.1, 47.4)	11.8 (4.6, 19.1)	61.0[d] (53.3, 68.7)	44.5[d] (36.7, 52.3)	10.4 (3.6, 17.2)
EASI-90[b]	38.6[e] (30.8, 46.3)	18.6[e] (12.5, 24.7)	5.3 (0.2, 10.3)	37.7[e] (30.0, 45.3)	23.9[e] (17.2, 30.6)	3.9 (0.0, 8.2)
PP-NRS (0 or 1)	35.4[e] (27.2, 43.6)	21.1[e] (13.9, 28.4)	3.2 (0.0, 7.5)	32.4[e] (24.5, 40.2)	21.3[e] (14.5, 28.0)	5.5 (0.3, 10.7)
PSAAD[f]	-3.2[d] (-3.6, -2.8)	-2.2[d] (-2.6, -1.9)	-1.1 (-1.7, -0.6)	-3.0[d] (-3.3, -2.7)	-2.4[d] (-2.8, -2.1)	-0.8 (-1.3, -0.3)

Abbreviations: CBQ=Cibinqo; 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; PSAAD=Pruritus and Symptoms Assessment for Atopic Dermatitis; QD=once daily.

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 ≥ 2 points.
b. EASI-75 and -90 responders were patients with ≥ 75% and ≥ 90% improvement, respectively, in EASI from baseline.
c. Cibinqo in monotherapy.
d. Statistically significant with adjustment for multiplicity versus placebo.
e. Statistically significant without adjustment for multiplicity versus placebo.
f. Results shown are least squares mean change from baseline.

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

	COMPARE[c]							
	Week 12				Week 16			
	CBQ + topicals		PBO + topicals N=131	DUP + topicals N=243	CBQ + topicals		PBO + topicals N=131	DUP + topicals N=243
	200 mg N=226	100 mg N=238			200 mg N=226	100 mg N=238		
	% Responders (95% CI)							
IGA 0 or 1[a]	48.4[d] (41.8, 55.0)	36.6[d] (30.4, 42.8)	14.0 (8.0, 19.9)	36.5 (30.4, 42.6)	47.5[d] (40.9, 54.1)	34.8[d] (28.6, 40.9)	12.9 (7.0, 18.8)	38.8 (32.5, 45.1)
EASI-75[b]	70.3[d] (64.3, 76.4)	58.7[d] (52.4, 65.0)	27.1 (19.5, 34.8)	58.1 (51.9, 64.3)	71.0[d] (65.1, 77.0)	60.3[d] (53.9, 66.6)	30.6 (22.5, 38.8)	65.5 (59.4, 71.6)
EASI-90[b]	46.1[e] (39.5, 52.7)	36.6[e] (30.4, 42.8)	10.1 (4.9, 15.3)	34.9 (28.8, 40.9)	48.9[e] (42.3, 55.5)	38.0[e] (31.7, 44.3)	11.3 (5.7, 16.9)	38.8 (32.5, 45.1)
PP-NRS (0 or 1)	36.9[e] (30.4, 43.3)	21.1[e] (15.7, 26.4)	7.4 (2.8, 12.1)	24.9 (19.2, 30.5)	32.0[e] (25.0, 38.9)	24.7[e] (18.2, 31.2)	11.7 (5.2, 18.2)	24.2 (18.1, 30.3)
PSAAD[f]	-3.6[e] (-3.8, -3.3)	-2.7[e] (-3.0, -2.5)	-1.6 (-2.0, -1.3)	-3.2 (-3.5, -3.0)	-3.6[e] (-3.8, -3.4)	-2.8[e] (-3.1, -2.6)	-1.7 (-2.0, -1.3)	-3.4 (-3.6, -3.2)

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

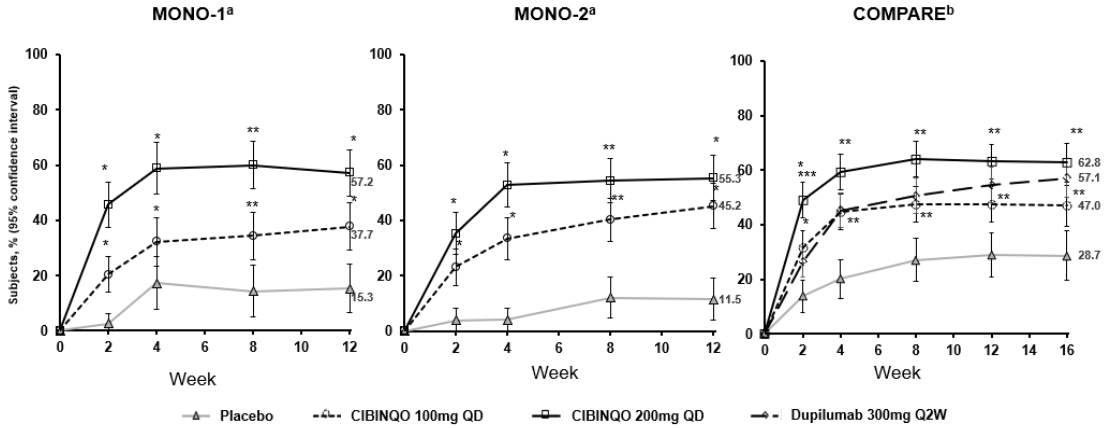
	COMPARE[c]							
	Week 12				Week 16			
	CBQ + topicals		PBO + topicals N=131	DUP + topicals N=243	CBQ + topicals		PBO + topicals N=131	DUP + topicals N=243
	200 mg N=226	100 mg N=238			200 mg N=226	100 mg N=238		

Abbreviations: CBQ=Cibinqo; 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; PSAAD=Pruritus and Symptoms Assessment for 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 ≥ 2 points.
b. EASI-75, -90 and responders were patients with ≥ 75% and ≥ 90% improvement, respectively, in EASI from baseline.
c. Cibinqo in combination with topical therapy.
d. Statistically significant with adjustment for multiplicity versus placebo.
e. Statistically significant without adjustment for multiplicity versus placebo.
f. Results shown are least squares mean change from baseline.

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.
PP-NRS4 responders were patients with ≥ 4-point improvement in Peak Pruritis Numerical Rating Scale (PP-NRS) from baseline.

a. Cibinqo used in monotherapy.
b. Cibinqo used in combination with medicated topical therapy.
* Statistically significant with adjustment for multiplicity versus placebo.
** Statistically significant without adjustment for multiplicity versus placebo.
***Statistically significant with adjustment for multiplicity versus dupilumab.

Health related outcomes

Treatment with either dose of Cibinqo as monotherapy or combination therapy resulted in improved patient-reported outcomes at 12 weeks compared with placebo. Higher proportions of the treatment groups had clinically meaningful reductions in DLQI total scores from baseline to Week 12 compared with placebo (defined as a 4-point improvement): 72.6-86.4% and 67.2-74.7% with 200 mg and 100 mg of medicinal product, respectively, versus 32.3-56.5% for placebo and separately, a DLQI score < 2 representing "no effect" of their disease on their quality of life (26.6-31.9% and 20.3-21.9% with 200 mg and 100 mg of medicinal product, respectively, versus 5.7-12.1% for placebo). Both groups also improved patient-reported atopic dermatitis symptoms, sleep disruption, and anxiety and depression symptoms compared with placebo at 12 weeks as measured by the Patient Oriented Eczema Measure (POEM) [least squares mean (LSM) changes were -10.6 to -12.6 and -6.8 to -9.6 for

Cibinqo 200 mg and 100 mg, respectively, compared with -3.6 to -5.1 for placebo], SCORing Atopic Dermatitis (SCORAD) sleep loss subscale (LSM changes were -3.7 to -4.6 and -2.1 to -3.8 with 200 mg and 100 mg of medicinal product, respectively, compared with -2.4 to -4.6 for placebo), and the Hospital Anxiety and Depression Scale (HADS) scores, respectively.

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, 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 Cibinqo in combination with topical therapy.

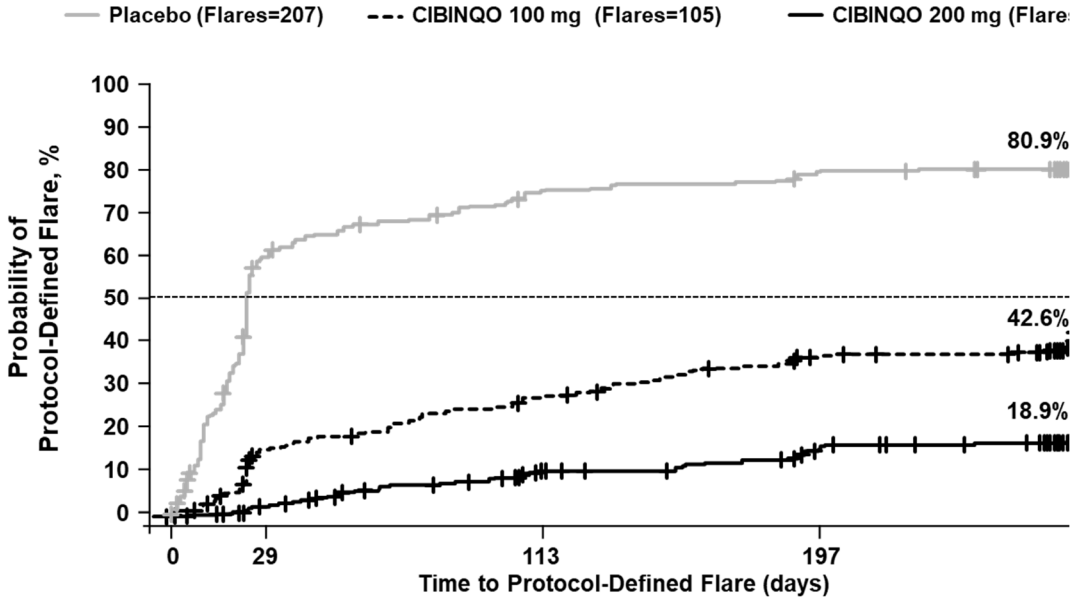
Table 5. Efficacy results of Cibinqo in REGIMEN

	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 ≥ 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 2. 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 versus placebo; 100 mg versus placebo; 200 mg versus 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.

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 Cibinqo 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, and the blind was maintained.

Among patients who achieved response after 12 weeks of treatment and entered EXTEND, the majority of patients maintained their response at Week 96 of cumulative treatment for both doses of Cibinqo [47% and 54% for IGA (0 or 1) response, 59% and 69% for EASI-75, and 50% and 60% for PP-NRS4 with 100 mg once daily and 200 mg once daily, respectively (using non-responder imputation)].

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 Cibinqo [22% and 27% for IGA (0 or 1) response, and 45% and 52% for EASI-75 with 100 mg once daily and 200 mg once daily, respectively (using non-responder imputation)].

Paediatric population

The Medicines and Healthcare products Regulatory Agency has deferred the obligation to submit the results of studies with Cibinqo in 1 or more subsets of the paediatric population in the treatment of atopic dermatitis (see section 4.2).

The efficacy and safety of Cibinqo 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 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 Cibinqo in combination with background medicated topical therapy was 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 ≥ 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 of Cibinqo in TEEN

	TEEN[d]		
	CBQ		PBO
	200 mg QD N=94	100 mg QD N=95	N=96
IGA 0 or 1[a] % responders (95% CI)	46.2[e] (36.1, 56.4)	41.6[e] (31.3, 51.8)	24.5 (15.8, 33.2)
EASI-75[b] % responders (95% CI)	72.0[e] (62.9, 81.2)	68.5[e] (58.9, 78.2)	41.5 (31.5, 51.4)
PP-NRS4[c] % responders (95% CI)	55.4[e] (44.1, 66.7)	52.6 (41.4, 63.9)	29.8 (20.0, 39.5)

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

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 ≥ 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.
d. Cibinqo used in combination with medicated topical therapy.
e. 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. Both C_{max} and AUC of abrocitinib increased dose proportionally up to 200 mg. Co-administration 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).

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 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.

In vitro, abrocitinib or its metabolites were not significant inhibitors or inducers of CYP enzymes (CYP2C8, CYP2C9, and CYP2D6) or of uridine diphosphate glucuronyltransferases (UGTs) (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7). Abrocitinib or its metabolites at clinically meaningful concentrations are not inhibitors of 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), organic anion transporting polypeptide (OATP) 1B1/1B3, bile salt export pump (BSEP), OAT1 or OCT2.

Elimination

The elimination half-life of abrocitinib is about 5 hours. Steady-state plasma concentrations of abrocitinib are achieved within 48 hours after once daily administration. Cibinqo 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).

Adolescents (≥ 12 to <18 years)
Based on population pharmacokinetic analysis, there was no clinically significant difference in mean Cibinqo 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 Cibinqo 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 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.

Cibinqo 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, Cibinqo 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

In toxicity studies of up to 1 month of Cibinqo 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

Cibinqo 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 Cibinqo 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. No evidence of abrocitinib-related thymoma was observed in females at exposures equal to 0.6 times the human AUC at the MRHD of 200 mg or in males 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

Cibinqo had no effects on male fertility or spermatogenesis. Abrocitinib resulted in effects on female fertility (lower fertility index, corpora lutea, implantation sites and postimplantation 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, no effects on embryo-foetal survival or foetal morphological development were noted at exposures equal to 4 times the unbound human AUC at the MRHD of 200 mg. Increased incidence of unossified forelimb phalanges was noted in the foetuses at exposures equal to 4 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 beginning on postnatal Day 21 and older (comparable to a 2-year-old human and older) was not associated with microscopic or macroscopic bone findings. Administration of abrocitinib to juvenile rats beginning on postnatal Day 10 (comparable to a 3-month-old human infant) resulted in adverse microscopic and macroscopic bone findings, including malrotated paws, fractures, and/or femoral head abnormalities.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Dibasic calcium phosphate anhydrous
Sodium starch glycolate
Magnesium stearate

Film-coat
Hypromellose
Titanium dioxide
Lactose monohydrate
Macrogol
Triacetin
Iron red oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

6.4 Special precautions for storage

Store below 30ºC.

Keep in original package.

6.5 Nature and contents of container

Polyvinylchloride (PVC)/ Polyvinylidene chloride (PVDC) foil blisters with aluminium foil lidding each containing 7 film-coated tablets. Each pack contains 28 film-coated tablets.

Not all pack sizes/strength may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Keep out of the sight and reach of children.

7 FURTHER INFORMATION
MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
UK

MANUFACTURER:
See outer pack.

8 DATE OF REVISION OF THE TEXT

August 2024

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep all medicaments out of reach and sight of children

Council of Arab Health Ministers

Union of Arabic Pharmacists