CIBINQO

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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 abrocitinib.

CIBINQO 100 mg film-coated tablets

Each film-coated tablet contains 100 mg abrocitinib.

CIBINQO 200 mg film-coated tablets

Each film-coated tablet contains 200 mg abrocitinib.

Excipient with known effect

Each CIBINQO 50 mg film-coated tablet contains 1.365 mg of lactose monohydrate.
Each CIBINQO 100 mg film-coated tablet contains 2.73 mg of lactose monohydrate.
Each CIBINQO 200 mg film-coated tablet contains 5.46 mg of lactose monohydrate.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

CIBINQO 50 mg film-coated tablets

Pink, oval tablet 10.50 mm long and 4.75 mm wide, debossed with “PFE” on one side and “ABR 50” on the other.

CIBINQO 100 mg film-coated tablets

Pink, round tablet 9.00 mm in diameter, debossed with “PFE” on one side and “ABR 100” on the other.

CIBINQO 200 mg film-coated tablets

Pink, oval tablet 18.42 mm long and 8.00 mm wide, 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 (age 18 years and above) who are candidates for systemic therapy and whose disease is not adequately controlled with topical medications or for whom topical treatments are otherwise medically inadvisable.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a healthcare professional experienced in the diagnosis and treatment of conditions for which CIBINQO is indicated (see Section 4.1).

Posology

The recommended dose of CIBINQO is 100 mg once daily. An initial dose of 200 mg once daily for 12 weeks followed by maintenance with 100 mg once daily may be appropriate for some patients who need rapid relief of symptoms. For most patients, 200 mg is the recommended starting dose. A dose of 100 mg once daily is the recommended starting dose for patients aged ≥65 years, and for those who have risk factors for developing an adverse reaction to abrocitinib or those who are less likely to tolerate the adverse reactions (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 used (see Section 5.1). The maximum daily dose is 200 mg.

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

Consider discontinuation of CIBINQO if adequate therapeutic benefit is not achieved after 24 weeks.

Treatment initiation
Treatment with CIBINQO 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, consider interruption of CIBINQO 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, resume dosing at the regular scheduled time.

Special dosage instructions

In patients receiving strong inhibitors of cytochrome P450 (CYP) 2C19 (e.g., fluvoxamine, fluconazole, fluoxetine and ticlopidine), the recommended 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., rifampin, apalutamide, efavirenz, enzalutamide, phenytoin) (see Section 4.5).

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 renal impairment (eGFR 30 to <60 mL/min), 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 renal impairment (eGFR <30 mL/min), the recommended starting dose of CIBINQO should be 50 mg once daily. The maximum daily dose is 100 mg. The dosing of CIBINQO in severe renal impairment patients is based on modelling and simulation which demonstrated comparability of active moiety exposures to patients with normal renal function administered doses of 100 mg and 200 mg once daily.

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 (see Section 5.2). CIBINQO must not be used in patients with severe (Child Pugh C) hepatic impairment (see Section 4.3).

Elderly population
The recommended starting dose for patients ≥65 years of age is 100 mg once daily (see Section 4.4). The risks and benefits of the recommended dose for patients ≥65 years of age should be considered (see Section 4.4). There are no conclusive data in patients 75 years of age and older.

Paediatric population
Use in paediatric patients under 12 years of age is not recommended.

Method of administration

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

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

CIBINQO tablets should be swallowed whole with water and should not be split, crushed, or chewed.

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 CIBINQO. 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).

The risks and benefits of treatment with CIBINQO should be carefully 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 CIBINQO. A patient who develops a new infection during treatment with CIBINQO should undergo prompt and complete diagnostic testing and appropriate antimicrobial therapy should be initiated. Discontinuation of CIBINQO should also be considered until the infection has resolved.

Tuberculosis
Tuberculosis was observed in clinical studies with abrocitinib. Patients should be screened for tuberculosis (TB) before starting CIBINQO therapy and consider yearly screening for patients in highly endemic areas for TB. CIBINQO 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 $<1 \times 10^3/mm^3$ 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 CIBINQO. 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 CIBINQO 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 with CIBINQO; such patients had HBV DNA monitored. If HBV DNA is detected, a liver specialist should be consulted.

Vaccination

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

Mortality

In a large, randomised, post-marketing safety study of another Janus kinase (JAK) inhibitor in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients treated with the JAK inhibitor compared with TNF blockers. CIBINQO is not approved for use in RA.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with CIBINQO.

Major adverse cardiovascular events

Major adverse cardiovascular events were reported in clinical studies of CIBINQO for atopic dermatitis (see Section 4.8).

In a large, randomised, post-marketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one 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 the JAK inhibitor compared to those treated with TNF blockers. CIBINQO is not approved for use in RA. Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with CIBINQO, particularly in patients who are current or past smokers and patients

with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue CIBINQO in patients that have experienced a myocardial infarction or stroke.

Thrombotic events including pulmonary embolism

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

In a large, randomised, post-marketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of overall thrombosis, DVT, and PE were observed compared to those treated with TNF blockers. CIBINQO is not approved for use in RA.

CIBINQO 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, CIBINQO treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.

Malignancy (including non-melanoma skin cancers)

Immunomodulatory drugs may increase the risk of malignancies including lymphoma. More cases of malignancies were observed with a JAK inhibitor other than CIBINQO compared with TNF inhibitors in the treatment of rheumatoid arthritis. 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.

Malignancies, including non-melanoma skin cancer (NMSC), were observed in clinical studies with CIBINQO for atopic dermatitis (see Section 4.8).

In a large, randomised, post-marketing safety study of another JAK inhibitor in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. CIBINQO is not approved for use in RA. A higher rate of lymphomas was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current or past smokers treated with the JAK inhibitor compared to those treated with TNF blockers. In this study, current or past smokers had an additional increased risk of overall malignancies.

The risks and benefits of CIBINQO 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 CIBINQO therapy in patients who develop a malignancy when on treatment, and patients who are current or past smokers. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Haematologic abnormalities

Confirmed ALC <0.5 × 10^3/mm^3 and platelet count <50 × 10^3/mm^3 were observed in less than 0.5% of patients in clinical studies. Treatment with CIBINQO should not be initiated in patients with a platelet count <150 × 10^3/mm^3, an ALC <0.5 × 10^3/mm^3, an ANC <1 × 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 with CIBINQO and thereafter according to routine patient management (see Table 1).

Lipids

In patients with a high burden of cardiovascular risk factors, including hyperlipidaemia, the risks and benefits of abrocitinib compared to that of other available therapies for atopic dermatitis should be considered. Dose-dependent increase in blood lipid parameters were reported in patients treated with CIBINQO (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 (see Table 1). The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined. More serious cardiac adverse events have been observed with a JAK inhibitor other than CIBINQO compared with TNF inhibitors in the treatment of rheumatoid arthritis. Patients with abnormal lipid parameters should be further monitored and managed according to clinical guidelines, due to the known cardiovascular risks associated with hyperlipidaemia. If abrocitinib is chosen, interventions to manage lipid concentrations should be implemented according to clinical guidelines.

Laboratory monitoring

Table 1. Laboratory 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 × 10^3/mm^3.
		ALC: Treatment should be interrupted if ALC is <0.5 × 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 × 10^3/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.

Elderly population

A total of 173 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 no conclusive data in patients above 75 years of age and older.

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. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicines to affect pharmacokinetics of CIBINQO

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 CIBINQO 100 mg was administered concomitantly with fluvoxamine (a strong CYP2C19 and moderate CYP3A inhibitor) or fluconazole (a strong CYP2C19, moderate CYP2C9 and CYP3A inhibitor), the extent of exposure of abrocitinib active moiety (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 CIBINQO 200 mg after multiple doses with rifampin, 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 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, a H2-receptor antagonist, the peak (C_{max}) and extent (AUC_{inf}) 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 medicines

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, may increase.

In vitro, abrocitinib is an inhibitor of CYP2C19 enzyme. Coadministration 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 metabolized by CYP2C19 enzyme (e.g., S-mephenytoin, clopidogrel).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data on the use of CIBINQO in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3). CIBINQO is contraindicated during pregnancy (see Section 4.3).

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 is encouraged.

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.

Fertility

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

4.7 Effects on ability to drive and use machines

No studies have been conducted on the effect of CIBINQO on driving ability or ability to operate machinery. CIBINQO has no or negligible sedating effect. Patients should be informed that dizziness has been reported during treatment with CIBINQO (see Section 4.8). 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 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%), vomiting (3.5%), dizziness (3.4%), blood creatine phosphokinase increased (3.1%), 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 CIBINQO in clinical studies in atopic dermatitis; among them 2,784 patients (representing 3,006 patient-years of exposure) were integrated for safety analysis, 1,451 patients with at least 48 weeks of exposure. The integrated safety analysis included 1,761 patients receiving a constant dose of abrocitinib 200 mg and 1,023 patients receiving 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			Thrombotic events[d]
Gastrointestinal disorders	Nausea (15.1%)	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. Thrombotic events 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% vs 1.4%), herpes zoster (1.2% and 0.6% vs 0%), pneumonia (0.1% and 0.1% vs 0%). Herpes simplex was more frequent in patients with a history of herpes simplex or eczema herpeticum. Most of the herpes zoster events involved a single dermatome and were non-serious.

Most opportunistic infections were cases of multidermatomal cutaneous herpes zoster (0.6%), most of which were non-serious. Among all patients treated with CIBINQO in the integrated safety analysis, including the long-term extension study, the rate of opportunistic infections was 0.61 per 100 patient-years in the CIBINQO 100 mg group and 1.23 per 100 patient-years) in the CIBINQO 200 mg group. Most cases of opportunistic herpes zoster were mild or moderate.

Among all patients treated with abrocitinib in the integrated safety analysis, 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 of herpes zoster were also higher for patients 65 years of age and older, patients with a medical history of herpes zoster, patients with severe atopic dermatitis at baseline, and a confirmed ALC $<1.0 \times 10^3/mm^3$ prior to the event of herpes zoster.

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 CIBINQO 100 mg, and 1.12 per 100 patient-years in patients treated with CIBINQO 200 mg. Among all patients treated with CIBINQO in the integrated safety analysis, including the long-term extension study, the rate of serious infections was 2.43 per 100 patient-years in the CIBINQO 100 mg group and 2.46 per 100 patient-years in the CIBINQO 200 mg group. The most commonly reported serious infections were herpes simplex, herpes zoster, and pneumonia (see Section 4.4).

Malignancy
In placebo-controlled studies, for up to 16 weeks, no malignancy was reported in subjects treated with placebo or CIBINQO 100 mg and in 1 patient (0.56 per 100 patient-years) treated with CIBINQO 200 mg. Among all patients treated with CIBINQO in the integrated safety analysis, including the long-term extension study, malignancy was reported in 4 subjects (0.5 per 100 patient-years) treated with CIBINQO 100 mg and 2 subjects (0.3 per 100 patient-years) treated with CIBINQO 200 mg.

Thrombotic events including pulmonary embolism
Among all patients treated with CIBINQO in the integrated safety analysis, including the long-term extension study, the rate of PE was 0.17 per 100 patient-years in the CIBINQO 200 mg group and 0.08 per 100 patient-years in the CIBINQO 100 mg group. The rate of DVT was 0.11 per 100 patient-years in the CIBINQO 200 mg group and 0 per 100 patient-years in the CIBINQO 100 mg group (see Section 4.4).

Major adverse cardiovascular events (MACE)
In placebo-controlled studies, for up to 16 weeks, major adverse cardiovascular event (MACE) was reported in 1 subject (0.55 per 100 patient-years) treated with CIBINQO 100 mg. Among all patients treated with CIBINQO in the integrated safety analysis, including the long-term extension study, MACE was reported in 2 patients (0.2 per 100 patient-years) treated with CIBINQO 100 mg and 4 subjects (0.2 per 100 patient-years) treated with CIBINQO 200 mg.

Thrombocytopenia
In placebo-controlled studies, for up to 16 weeks, treatment with CIBINQO 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 exposed to CIBINQO 200 mg, and 0 patients treated with CIBINQO 100 mg or placebo. Among all patients exposed to CIBINQO in the integrated safety analysis, including the long-term extension study, the rate of confirmed platelet counts of $<50 \times 10^3/mm^3$ 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 $<75 \times 10^3/mm^3$ (see Section 4.4). There were no adolescent patients who developed platelet counts $<75 \times 10^3/mm^3$.

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 CIBINQO 200 mg and 0% of patients treated with CIBINQO 100 mg or placebo. Both cases occurred in the first 4 weeks of exposure. Among all patients exposed to CIBINQO in the integrated safety analysis, including the long-term extension, the rate of confirmed ALC $<0.5 \times 10^3/mm^3$ 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). 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 percent 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. 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. 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, events of blood CPK increased (>5 × ULN) were reported in 3.8% of patients treated with 200 mg of CIBINQO, 1.8% of patients treated with 100 mg of CIBINQO and 1.8% of patients treated with placebo. Most elevations were transient, and none led to discontinuation.

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

Psychiatric disorders
Patients who showed suicidal ideation(s)/behaviour(s) in relevant preliminary investigations were excluded from the clinical trials.

<u>Adolescent population</u>

A total of 635 adolescents (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 (see Section 4.2).

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. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

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

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

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 pathway by preventing the phosphorylation and activation of STATs.

In biochemical assay, abrocitinib has selectivity for JAK1 over the other 3 JAK isoforms JAK2 (28-fold), JAK3 (>340-fold) and tyrosine kinase 2 (TYK 2, 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

Clinical biomarkers
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.

Blood counts
Mean ALC 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 CIBINQO on the QTc interval was examined in subjects who received single doses of abrocitinib 600 mg in a placebo- and positive-controlled thorough QT study. In a concentration-QTc analysis, abrocitinib at therapeutic and supratherapeutic plasma concentrations did not lead to a prolongation of the QTc intervals.

Clinical efficacy and safety

The efficacy and safety of CIBINQO as monotherapy and in combination with background medicated topical therapies over 12 to 16 weeks were evaluated in 1,616 patients in 3 pivotal Phase 3 randomised, double-blind, placebo-controlled studies (MONO-1, MONO-2, and COMPARE). In addition, the efficacy and safety of CIBINQO in monotherapy over 52 weeks (with the option of rescue treatment in flaring subjects) was evaluated in 1,233 subjects in a Phase 3 induction, randomised withdrawal, double-blind, placebo-controlled study (REGIMEN). The patients in these 4 studies had moderate-to-severe atopic dermatitis as defined by Investigator's Global Assessment (IGA) score ≥3, Eczema Area and Severity Index (EASI) score ≥16, body surface area (BSA) involvement ≥10%, and Peak Pruritus Numerical Rating Scale (PP-NRS) ≥4 at baseline visit 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 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).

A significantly greater proportion of patients achieved at least a PP-NRS 4-point improvement with CIBINQO 100 mg or 200 mg once daily compared with placebo. This 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 monotherapy at Week 12

	MONO-1[c]			**MONO-2[c]**		
	CBQ monotherapy			**CBQ monotherapy**		
	200 mg QD N=154	**100 mg QD N=156**	**Placebo N=77**	**200 mg QD N=155**	**100 mg QD N=158**	**Placebo N=78**
	% Responders (95% CI)					
IGA 0 or 1[a]	43.8[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)
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's Global Assessment; N=number of patients randomised; PP-NRS=Peak Pruritus Numerical Rating Scale; PSAAD=Pruritus and Symptoms Assessment for Atopic Dermatitis; QD=once daily.

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. CIBINQO in monotherapy.
d. Statistically significant with adjustment for multiplicity vs placebo.
e. Statistically significant without adjustment for multiplicity vs 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

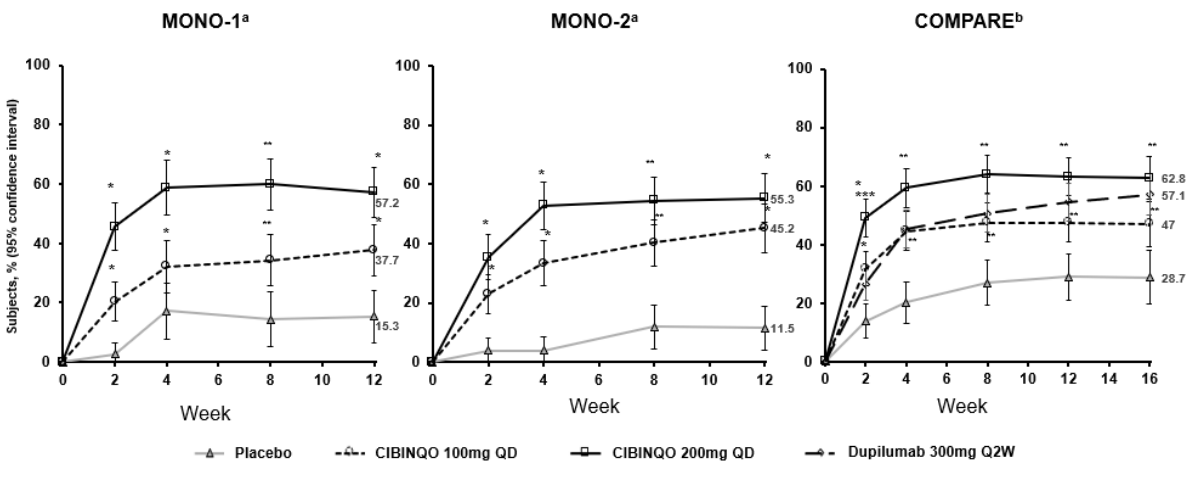
	COMPARE[c]							
	Week 12				Week 16			
	CBQ + topicals		PBO + topicals N=131	DUP + topicals N=243	CBQ + topicals		PBO + topicals N=131	DUP + topicals N=243
	200 mg N=226	100 mg N=238			200 mg N=226	100 mg N=238		
	% Responders (95% CI)							
IGA 0 or 1[a]	48.4[d] (41.8, 55.0)	36.6[d] (30.4, 42.8)	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)
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)

Abbreviations: CBQ=CIBINQO; CI=confidence interval; DUP=Dupilumab; EASI=Eczema Area and Severity Index; IGA=Investigator's 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 responders were patients with ≥75% improvement in EASI from baseline.
c. CIBINQO in combination with topical therapy.
d. Statistically significant with adjustment for multiplicity vs placebo.
e. Statistically significant without adjustment for multiplicity vs 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 Pruritus 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 vs placebo.
** Statistically significant without adjustment for multiplicity vs placebo.
*** Statistically significant with adjustment for multiplicity vs dupilumab.

Health-related outcomes

Both the 100 mg and 200 mg doses of CIBINQO, whether as monotherapy or combination therapy, led to a higher proportion of patients with reductions in DLQI than placebo at 12 weeks. Patients also had improved symptoms of atopic dermatitis, sleep disturbances, and anxiety and depression symptoms, from the patient's perspective, as measured by the Patient Oriented Eczema Measure (POEM) after 12 weeks, the sleep loss subscale of the SCORing Atopic Dermatitis (SCORAD) and the Hospital Anxiety and Depression Scale (HADS) scores.

Dose reduction: 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.

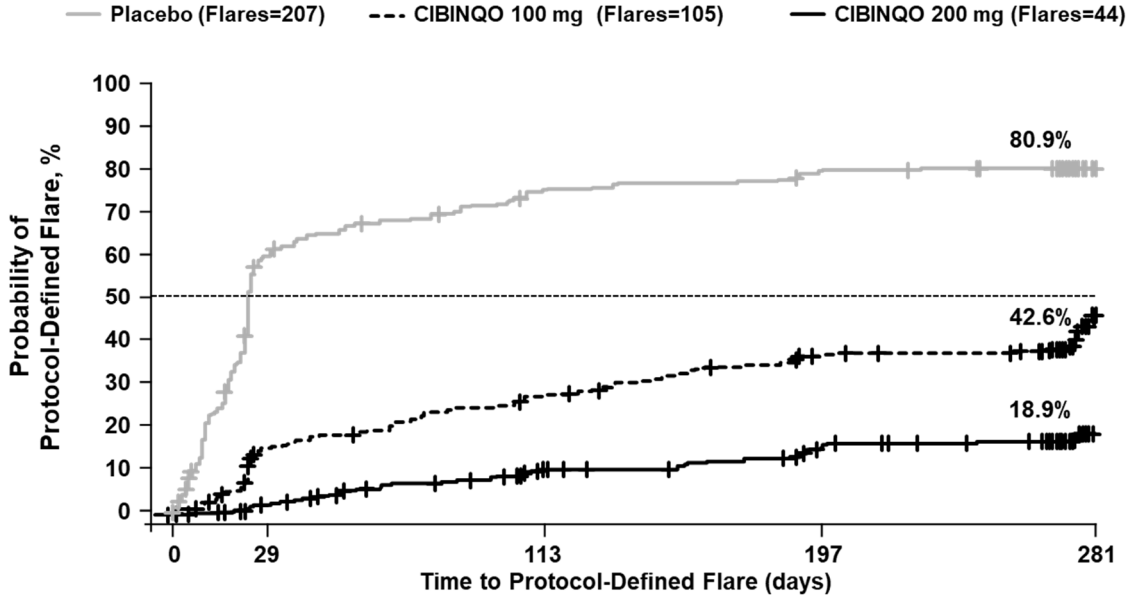
Table 5. Efficacy results of CIBINQO in REGIMEN

	CBQ monotherapy Open-label induction, Week 12 200 mg N=1,233
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 vs placebo; 100 mg vs placebo; 200 mg vs 100 mg.

A multivariate analysis was performed to identify predictors of successfully decreasing the dose from 200 mg to 100 mg and remaining flare-free for at least 12 weeks after the dose decrease. In that analysis, patients who had not received prior systemic agents (OR 1.8, 95% CI: 1.2, 2.6) and patients who had ≤50% BSA involvement before starting abrocitinib (OR 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 enrollment 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

CIBINQO 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 48 of cumulative CIBINQO treatment for both doses of CIBINQO [53% and 57% for IGA (0 or 1) response, 69% and 71% for EASI-75, and 52% and 69% 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 CIBINQO 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 54% for EASI-75 with 100 mg once daily and 200 mg once daily, respectively].

Patients who received dupilumab in the COMPARE study and subsequently entered EXTEND were randomised to either 100 mg or 200 mg of CIBINQO once daily upon entering EXTEND. Among non-responders to dupilumab, a substantial proportion of patients achieved response 12 weeks after switching to CIBINQO [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].

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 from 30 to 400 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 radiolabeled 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 (11%) and M4 (24%) are major metabolites and M1 (9.6%) 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 total body clearance of abrocitinib is 22 L/hr. 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. Abrocitinib is eliminated primarily by metabolic clearance mechanisms, with less than 1% of the dose excreted in urine as unchanged drug. The urinary excretion of the metabolites of abrocitinib is 16%, 14% and 15% of the administered abrocitinib dose for M1, M2 and M4, respectively, and the metabolites are substrates of OAT3 transporter. As a percent of total clearance, the renal elimination for M1 is 74% and >90% for M2 and M4, while the faecal elimination of M1, M2, and M4 are 8%, 4%, and 2% respectively.

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 significant difference in mean abrocitinib steady-state exposures in adolescent patients compared to adults at their typical body weights.

Paediatric (<12 years)
The pharmacokinetics of CIBINQO in paediatric patients 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, CIBINQO was not evaluated in patients with atopic dermatitis with baseline creatinine clearance values less than 40 mL/min.

Hepatic impairment

Patients with mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment had approximately 4% decrease and 15% increase in active moiety AUC_{inf}, respectively, compared to patients with normal hepatic function. These changes are not clinically significant, and no dose adjustment is required in patients with mild or moderate hepatic impairment (see Section 4.2). 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 initiated at 6-8 weeks and 9-weeks of age, a bone dystrophy finding was noted, at exposure of greater than or equal to 22 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 (up to 30 times the human AUC at the MRHD of 200 mg).

Genotoxicity

CIBINQO is not mutagenic in the bacterial mutagenicity assay (Ames assay). Although CIBINQO is aneugenic in the *in vitro* TK6 micronucleus assay, CIBINQO is 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 for 26 weeks at exposures equal to 0.6 and 0.2 times the human AUC at the MRHD of 200 mg in female and male mice, respectively. In the 2-year oral carcinogenicity study, CIBINQO resulted in a statistically higher incidence of benign thymomas in female rats at exposures greater than or equal to 2.7 times the human AUC at the MRHD of 200 mg. No evidence of CIBINQO-related tumorigenicity was observed following oral CIBINQO administration in female rats at exposures equal to 0.6 times the human AUC at the MRHD of 200 mg or in male rats at exposures equal to 13 times the human AUC at the MRHD of 200 mg.

Reproductive and developmental toxicity

CIBINQO had no effects on rat male fertility or spermatogenesis at doses up to 70 mg/kg/day at exposures equal to 25 times the human AUC at the MRHD of 200 mg. CIBINQO resulted in effects on rat female fertility (lower fertility index, corpora lutea, and implantation sites) at exposures equal to 28 times the human AUC at the MRHD of 200 mg and higher postimplantation loss at exposures greater than or equal to 10 times the human AUC at the MRHD of 200 mg. The effects on female fertility reversed 1 month after cessation of CIBINQO administration. No effects on female fertility were noted at exposures equal to 1.9 times the human AUC at the MRHD of 200 mg.

No foetal malformations were observed in embryo-foetal development studies in rats or rabbits. In an embryo-foetal development study in pregnant rabbits, oral administration of CIBINQO during gestation days 7 to 19 had no effects on embryo-foetal survival or foetal morphological development at exposures equal to 7.6 times the human AUC at the MRHD of 200 mg. CIBINQO resulted in increased incidence of unossified forelimb phalanges at exposures equal to 7.6 times the human AUC at the MRHD of 200 mg.

In an embryo-foetal development study in pregnant rats, oral administration of CIBINQO during gestation days 6 to 17 resulted in increased embryo-foetal lethality at exposures equal to 16 times the human AUC at the MRHD of 200 mg. No embryo-foetal lethality was observed in pregnant rats orally dosed with CIBINQO during organogenesis at exposures equal to 10 times the human AUC at the MRHD of 200 mg. CIBINQO resulted in increased incidences of skeletal variations of short 13^{th} ribs at exposures greater than or equal to 10 times the human AUC at the MRHD of 200 mg and reduced ventral processes, thickened ribs, and unossified metatarsals were observed at exposures equal to 16 times the human AUC at the MRHD of 200 mg. No skeletal variations were noted in rats 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, oral administration of CIBINQO during gestation day 6 through lactation day 21 resulted in dystocia with prolonged parturition and lower offspring body weights at exposures greater than or equal to 10 times the human AUC at the MRHD of 200 mg and lower postnatal survival at exposures equal to 16 times the human AUC at the MRHD of 200 mg. 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 greater than or equal to 0.8 times the unbound 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.

Juvenile animal toxicity

In the juvenile rat study, oral administration of CIBINQO to rats initiated at postnatal Day 10 resulted in bone findings (malrotated and/or impaired use of the forelimbs, hindlimbs, or paws, fractures and/or abnormalities of the femoral head, and bony dystrophy), at exposures

≥0.8 times the human AUC at the MRHD of 200 mg. Irreversible low femur length and width were observed at exposures 26 times the human AUC at the MRHD of 200 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Dibasic calcium phosphate anhydrous
Sodium starch glycolate
Magnesium stearate

Film-coat

Hypromellose (E464)
Titanium dioxide (E171)
Lactose monohydrate
Macrogol/PEG
Triacetin (E1518)
Iron red oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Refer to outer carton.

6.4 Special precautions for storage

Keep in original package.

6.5 Nature and contents of container

CIBINQO 50 mg 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

Polyvinylidene chloride 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

Polyvinylidene chloride 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.

6.6 Special precautions for disposal and other handling

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

7. PRODUCT OWNER

Pfizer Inc.
235 East 42nd Street
New York, NY 10017
United States

ABRO-SIN-0223/0
Date of last revision: February 2023

Package leaflet: information for the patient

CIBINQO™ 50 mg film-coated tablets
CIBINQO™ 100 mg film-coated tablets
CIBINQO™ 200 mg film-coated tablets
abrocitinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What CIBINQO is and what it is used for

CIBINQO contains the active substance abrocitinib. It belongs to a group of medicines called Janus kinase inhibitors, which help to reduce inflammation. It works by reducing the activity of an enzyme in the body called 'Janus kinase', which is involved in inflammation.

CIBINQO is used to treat adults with moderate-to-severe atopic dermatitis, also known as atopic eczema. By reducing the activity of Janus kinase enzymes, CIBINQO lessens itching and inflammation of the skin. This in turn can reduce sleep disturbances and other consequences of atopic eczema such as anxiety or depression and improves overall quality of life.

2. What you need to know before you take CIBINQO

Do not take CIBINQO
- if you are allergic to abrocitinib or any of the other ingredients of this medicine (listed in section 6).
- if you have a serious infection ongoing, including tuberculosis.
- if you have severe liver problems.

- if you are pregnant or breast-feeding (see the "pregnancy, contraception, breast-feeding and fertility" section).

Warnings and precautions
Talk to your doctor or pharmacist before and during treatment with CIBINQO if you:
- have an infection or if you often get infections. Tell your doctor if you get symptoms such as fever, sweating, or chills, muscle aches, cough or shortness of breath, blood in your phlegm, weight loss, diarrhoea or stomach pain, burning when you urinate or urinating more often than usual, wounds, feeling more tired than usual or dental problems as these can be signs of infection. CIBINQO can reduce your body's ability to fight infections and may make an existing infection worse or increase the chance of you getting a new infection.
- have, or have had, tuberculosis or have been in close contact with someone with tuberculosis. Your doctor will test you for tuberculosis before starting CIBINQO and may retest during treatment.
- have ever had a herpes infection (shingles), because CIBINQO may allow it to come back. Tell your doctor if you get a painful skin rash with blisters as this can be a sign of shingles.
- have eczema herpeticum (skin infection caused by herpes simplex virus), which presents as itchy and painful red spots that spreads quickly throughout the body.
- have ever had hepatitis B or hepatitis C.
- have recently had or plan to have a vaccination (immunisation) - this is because certain vaccines (live, attenuated vaccines) are not recommended while using CIBINQO.
- have previously had blood clots in the veins of your legs (deep vein thrombosis) or lungs (pulmonary embolism) or have an increased risk for developing this (for example: if you had recent major surgery or if you use hormonal contraceptives/hormonal replacement therapy. Your doctor will discuss with you if CIBINQO is appropriate for you. Tell your doctor if you get sudden shortness of breath or difficulty breathing, chest pain or pain in upper back, swelling of the leg or arm, leg pain or tenderness, or redness or discolouration in the leg or arm as these can be signs of blood clots in the veins.
- have or have had cancer, smoke or have smoked in the past – your doctor will discuss with you if CIBINQO is appropriate for you.
- Non-melanoma skin cancer has been observed in patients taking CIBINQO. Your doctor may recommend that you have regular skin examinations while taking CIBINQO. If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.
- have, or had heart problems, or other medical conditions such as elevated blood cholesterol that make you more likely to develop heart disease – your doctor will discuss with you if CIBINQO is appropriate for you.

<u>Additional monitoring tests</u>
Your doctor will carry out blood tests before and during CIBINQO treatment and may adjust your treatment if necessary.

Children
This medicine is not approved for use in children below the age of 18 years because the safety and benefits of CIBINQO are not yet fully established.

Other medicines and CIBINQO
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor or pharmacist before taking CIBINQO if you are taking some of the medicines to treat:

- fungal infections (such as fluconazole), depression (such as fluoxetine or fluvoxamine), stroke (such as ticlopidine), as they may increase the side effects of CIBINQO.
- stomach acid reflux (such as antacids, famotidine or omeprazole), as they may reduce the amount of CIBINQO in your blood.
- heart failure (such as digoxin) or stroke (such as dabigatran), as CIBINQO may increase their effects.
- seizures (such a S-mephenytoin), as CIBINQO may increase its effects.
- stroke (such as clopidogrel), as CIBINQO may increase its effects.

Your doctor can tell you to avoid using or stop taking CIBINQO if you are taking some of the medicines to treat:

- tuberculosis (such as rifampin), seizures or fits (such as phenytoin), prostate cancer (such as apalutamide, enzalutamide), or HIV infection (such as efavirenz), as these may reduce how well CIBINQO works.

If any of the above apply to you or if you are not sure, talk to your doctor or pharmacist before taking CIBINQO.

Pregnancy, contraception, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Contraception in women
If you are a woman of childbearing potential, you should use an effective method of contraception during treatment with CIBINQO, and for at least one month after your last treatment dose. Your doctor can advise you on suitable methods of contraception.

Pregnancy
Do not use CIBINQO if you are pregnant, think you may be pregnant or are planning to have a baby since it can harm the developing baby. Tell your doctor right away if you become pregnant or think you might have become pregnant during treatment.

Breast-feeding
Do not use CIBINQO while breast-feeding as it is not known if this medicine passes into breast milk and affects the baby. You and your doctor should decide if you will breast-feed or use this medicine.

Fertility
CIBINQO may cause temporary reduced fertility in woman of childbearing potential. This effect is reversible after stopping treatment.

Driving and using machines
CIBINQO has no effect on the ability to drive or use machines. However, some individuals may experience dizziness. If you experience dizziness after taking CIBINQO, you should not drive or operate machines until the dizziness resolves.

CIBINQO contains lactose monohydrate and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

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

3. How to take CIBINQO

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

CIBINQO is a tablet to be taken by mouth. It may be used with other eczema medicines that you apply on the skin or it may be used on its own.

For most patients, the recommended starting dose is 200 mg once a day. Some patients need a lower starting dose and your doctor may give you 100 mg once a day if you are 65 years of age and older, or if you have a certain medical history or medical condition. If you have moderate-to-severe kidney problems, or if you are prescribed certain other medicines the starting dose can be either 50 mg or 100 mg once a day. You will get a starting dose based on your need and medical history, and therefore you should always take this medicine exactly as your doctor has told you.

Maximum daily dose is 200 mg. In patients with severe renal impairment, the maximum daily dose is 100 mg.

After starting treatment, your doctor can adjust the dose based on how well the medicine works and any side effect you get. If the medicine is working well, the dose may be reduced. Treatment may also be stopped temporarily or permanently if blood tests show low white blood cell or platelet counts.

If you have taken CIBINQO for 24 weeks and still show no improvement, your doctor may decide to permanently stop the treatment.

You should swallow your tablet whole with water. Do not split, crush or chew the tablet before swallowing as it may change how much medicine that gets into your body.

You can take the tablet either with or without food. If you feel sick (nausea) when taking this medicine, it may help to take it with food. To help you remember to take your medicine, it is suggested that you take it the same time every day.

If you take more CIBINQO than you should
If you take more CIBINQO than you should, contact your doctor. You may get some of the side effects described in section 4.

If you forget to take CIBINQO
- If you miss a dose, take it as soon as you remember, unless your next dose is due in less than 12 hours.
- If there is less than 12 hours before your next dose, just skip the missed dose and take your next usual dose when it is due.
- Do not take a double dose to make up for a forgotten tablet.

If you stop taking CIBINQO
You should not stop taking CIBINQO without discussing this with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Talk to your doctor and get medical help straight away if you get any signs of:
- Shingles (herpes zoster), a painful skin rash with blisters and fever
- Blood clots in the lungs, legs or pelvis with symptoms such as a painful swollen leg, chest pain or shortness of breath

Other side effects

Very common (may affect more than 1 in 10 people)
- Feeling sick (nausea)

Common (may affect up to 1 in 10 people)
- Cold sores and other types of herpes simplex infections
- Low platelet count shown by blood test
- Headache
- Dizziness
- Vomiting
- Stomach pain
- Acne
- Increase in an enzyme called creatine phosphokinase, shown by blood test

Uncommon (may affect up to 1 in 100 people)
- Pneumonia (lung infection)
- Low white blood cell count shown by blood test
- High blood fat (cholesterol) shown by blood test (see section 2 Warnings and precautions)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store CIBINQO

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister foil after EXP.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What CIBINQO contains

- The active substance is abrocitinib.
  Each 50 mg tablet contains 50 mg of abrocitinib.
  Each 100 mg tablet contains 100 mg of abrocitinib.
  Each 200 mg tablet contains 200 mg of abrocitinib.

- The other ingredients are:
  Tablet core: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, magnesium stearate.
  Film coat: hypromellose (E464), titanium dioxide (E171), lactose monohydrate, macrogol/PEG, triacetin (E1518), iron red oxide (E172) (see section 2 CIBINQO contains lactose and sodium).

What CIBINQO looks like and contents of the pack

CIBINQO 50 mg tablets are pink, oval tablets 10.50 mm long and 4.75 mm wide, with “PFE” on one side and “ABR 50” on the other.

CIBINQO 100 mg tablets are pink, round tablets 9.00 mm in diameter, with “PFE” on one side and “ABR 100” on the other.

CIBINQO 200 mg tablets are pink, oval tablets 18.42 mm long and 8.00 mm wide, with “PFE” on one side and “ABR 200” on the other.

The 50 mg, 100 mg and 200 mg tablets are provided in polyvinylidene chloride (PVDC) blisters with aluminum foil lidding film. Each blister pack contains 14, 28 or 91 tablets.

Not all pack sizes may be marketed.

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