ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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, approximately 11 mm long and 5 mm wide oval tablet debossed with “PFE” on one side and “ABR 50” on the other.

Cibinqo 100 mg film-coated tablets

Pink, approximately 9 mm in diameter round tablet debossed with “PFE” on one side and “ABR 100” on the other.

Cibinqo 200 mg film-coated tablets

Pink, approximately 18 mm long and 8 mm wide 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 is 100 mg or 200 mg once daily based on individual patient characteristics:

- A starting dose of 100 mg once daily is recommended for patients at higher risk of venous thromboembolism (VTE), major adverse cardiovascular event (MACE) and malignancy (see section 4.4). If the patient does not respond adequately to 100 mg once daily, the dose can be increased to 200 mg once daily.
- 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. In adolescents (12 years to 17 years of age), weighing 25 kg to < 59 kg, a starting dose of 100 mg once a day is recommended. If the patient does not respond adequately to 100 mg once daily, the dose can be increased to 200 mg once daily. In adolescents weighing at least 59 kg, a starting dose of 100 mg or 200 mg once daily may be appropriate.

The lowest effective dose for maintenance should be considered.

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

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

Laboratory monitoring

Table 1. Laboratory measures and monitoring guidance

Laboratory measures	Monitoring guidance	Action
Complete blood count including Platelet Count, Absolute Lymphocyte Count (ALC), Absolute Neutrophil Count (ANC) and Haemoglobin (Hb)	Before treatment initiation, 4 weeks after initiation and thereafter according to routine patient management.	Platelets: Treatment should be discontinued if platelet counts are $< 50 \times 10^3/mm^3$.
		ALC: Treatment should be interrupted if ALC is $< 0.5 \times 10^3/mm^3$ 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 is < 8 g/dL and may be restarted once Hb returns above this value.
Lipid parameters	Before treatment initiation, 4 weeks after initiation and thereafter according to the patient's risk for cardiovascular disease and clinical guidelines for hyperlipidaemia.	Patients should be monitored according to clinical guidelines for hyperlipidaemia.

Treatment initiation
Treatment should not be initiated in patients with a platelet count $< 150 \times 10^3/mm^3$, an absolute lymphocyte count (ALC) $< 0.5 \times 10^3/mm^3$, an absolute neutrophil count (ANC) $< 1.2 \times 10^3/mm^3$ or who have a haemoglobin value < 10 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.

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

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

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

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

Special populations

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

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

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

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

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

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

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

Method of administration

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

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Abrocitinib should only be used if no suitable treatment alternatives are available in patients: -65 years of age and older; -patients with 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 history of malignancy)

Infections/serious infections

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

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 abrocitinib should be considered for patients:

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

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

Tuberculosis
Tuberculosis was observed in clinical studies with abrocitinib. Patients should be screened for TB before starting treatment and yearly screening for patients in highly endemic areas for TB should be considered. Abrocitinib must not be given to patients with active TB (see section 4.3). For patients with a new diagnosis of latent TB or prior untreated latent TB, preventive therapy for latent TB should be started prior to initiation of treatment.

Viral reactivation
Viral reactivation, including herpes virus reactivation (e.g. herpes zoster, herpes simplex), was reported in clinical studies (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.

Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy and during therapy. Patients with evidence of active hepatitis B or hepatitis C (positive hepatitis C PCR) infection were excluded from clinical studies (see section 5.2). Patients who were hepatitis B surface antigen negative, hepatitis B core antibody positive, and hepatitis B surface antibody positive had testing for hepatitis B virus (HBV) DNA. Patients who had HBV DNA above the lower limit of quantification (LLQ) were excluded. Patients who had HBV DNA negative or below

LLQ could initiate treatment; such patients had HBV DNA monitored. If HBV DNA is detected, a liver specialist should be consulted.

Vaccination

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

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 randomized 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 randomized 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 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 randomized 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 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 abrocitinib 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 < $1.2 \times 10^3/mm^3$ or who have a haemoglobin value < 10 g/dL (see section 4.2). Complete blood count should be monitored 4 weeks after initiation of therapy and thereafter according to routine patient management (see Table 1).

Lipids

Dose-dependent increases in blood lipid parameters were reported in patients treated with abrocitinib compared to placebo (see section 4.8). Lipid parameters should be assessed approximately 4 weeks following initiation of therapy and thereafter according to the patient's risk for cardiovascular disease (see Table 1). The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined. Patients with abnormal lipid parameters should be further monitored and managed according to clinical guidelines, due to the known cardiovascular risks associated with hyperlipidaemia.

Elderly

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

Immunosuppressive conditions or medicinal products

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

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

Excipients

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicines to affect pharmacokinetics of abrocitinib

Abrocitinib is metabolised predominantly by CYP2C19 and CYP2C9 enzymes, and to a lesser extent by CYP3A4 and CYP2B6 enzymes, and its active metabolites are renally excreted and are substrates of the organic anion transporter 3 (OAT3). Therefore, exposures of abrocitinib and/or its active metabolites may be affected by medicinal products that inhibit or induce these enzymes and transporter. Dose adjustments, as appropriate, are outlined in section 4.2.

Co-administration with CYP2C19/CYP2C9 inhibitors

When 100 mg abrocitinib was administered concomitantly with fluvoxamine (a strong CYP2C19 and moderate CYP3A inhibitor) or fluconazole (a strong CYP2C19, moderate CYP2C9 and CYP3A inhibitor), the extent of exposure of abrocitinib active moiety (see section 5.2) increased by 91% and 155%, respectively, compared with administration alone (see section 4.2).

Co-administration with CYP2C19/CYP2C9 inducers

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

Co-administration with OAT3 inhibitors

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

Co-administration with products which increase gastric pH

When abrocitinib 200 mg was administered concomitantly with famotidine 40 mg, an H2-receptor antagonist, abrocitinib active moiety exposures decreased by approximately 35%. The effect of elevating gastric pH with antacids, or proton pump inhibitors (omeprazole) on the pharmacokinetics of abrocitinib has not been studied and may be similar to that seen with famotidine. The higher 200 mg daily dose should be considered for patients treated concomitantly with products which increase gastric pH, as they may reduce the efficacy of abrocitinib.

Potential for abrocitinib to affect pharmacokinetics of other medicinal products

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

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

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

There are no or limited amount of data on the use of abrocitinib in pregnant women. Studies in animals have shown reproductive toxicity. Abrocitinib has been shown to cause embryo-foetal lethality in pregnant rats and rabbits, skeletal variations in the 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 influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are nausea (15.1%), headache (7.9%), acne (4.8%), herpes simplex (4.2%), blood creatine phosphokinase increased (3.8%), vomiting (3.5%), dizziness (3.4%) and abdominal pain upper (2.2%). The most frequent serious adverse reactions are infections (0.3%) (see section 4.4).

Tabulated list of adverse reactions

A total of 3 848 patients were treated with abrocitinib in clinical studies in atopic dermatitis. Among them 3 050 patients (representing 5 166 patient-years of exposure) were integrated for safety analysis. The integrated safety analysis included 1 997 patients receiving a constant dose of abrocitinib 200 mg and 1 053 patients receiving a constant dose of 100 mg. There were 2 013 patients with at least 48 weeks of exposure. Five placebo-controlled studies were integrated (703 patients on 100 mg once daily, 684 patients on 200 mg once daily and 438 patients on placebo) to evaluate the safety of abrocitinib in comparison to placebo for up to 16 weeks.

Listed in Table 2 are adverse reactions observed in atopic dermatitis clinical studies presented by system organ class and frequency, using the following categories: very common (≥ 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 Neutropenia[c]
Metabolism and nutrition disorders			Hyperlipidaemia[d]
Nervous system disorders		Headache Dizziness	
Vascular disorders			Venous thromboembolism[e]
Gastrointestinal disorders	Nausea	Vomiting Abdominal pain upper	
Skin and subcutaneous tissue disorders		Acne	
Investigations		Creatine phosphokinase increased > 5 × ULN[f]	

a. Herpes simplex includes oral herpes, ophthalmic herpes simplex, genital herpes, and herpes dermatitis.
b. Herpes zoster includes ophthalmic herpes zoster.
c. Neutropenia includes neutrophil count decreased and granulocytopenia.
d. Hyperlipidaemia includes dyslipidaemia and hypercholesterolaemia.
e. Venous thromboembolism includes pulmonary embolism and deep vein thrombosis.
f. Includes changes detected during laboratory monitoring (see text below).

Description of selected adverse reactions

Infections
In placebo-controlled studies, for up to 16 weeks, infections have been reported in 27.4% of patients treated with placebo and in 34.9% and 34.8% of patients treated with abrocitinib 100 mg and 200 mg, respectively. Most infections were mild or moderate. The percentage of patients reporting infection-related adverse reactions in the 200 mg and 100 mg groups compared to placebo were: herpes simplex (4.2% and 2.8% versus 1.4%), herpes zoster (1.2% and 0.6% versus 0%), pneumonia (0.1% and 0.1% versus 0%). Herpes simplex was more frequent in patients with a history of herpes simplex or eczema herpeticum. Most of the herpes zoster events involved a single dermatome and were non-serious. Most opportunistic infections were cases of herpes zoster (0.70 per 100 patient-years in the abrocitinib 100 mg group and 0.96 per 100 patient-years in the abrocitinib 200 mg group), most of which were non-serious multidermatomal cutaneous infections. Among all patients treated in clinical studies with consistent dosing regimens of either abrocitinib 100 mg or 200 mg, including the long-term extension study, the incidence rate of herpes zoster in patients treated with abrocitinib 200 mg (4.36 per 100 patient-years) was higher than that of patients treated with 100 mg (2.61 per 100 patient-years). Incidence rates for herpes zoster were also higher for patients 65 years of age and older (HR 1.76), patients with a medical history of herpes zoster (HR 3.41), patients with severe atopic dermatitis at baseline (HR 1.17), and a confirmed ALC < $1.0 \times 10^3/mm^3$ prior to the event of herpes zoster (HR 2.18) (see section 4.4).

In placebo-controlled studies, for up to 16 weeks, the rate of serious infections was 1.81 per 100 patient-years in patients treated with placebo, 3.32 per 100 patient-years in patients treated with 100 mg, and 1.12 per 100 patient-years in patients treated with 200 mg. Among all patients treated in clinical studies with consistent dosing regimens of either abrocitinib 100 mg or 200 mg, including the long-term extension study, the rate of serious infections was 2.20 per 100 patient-years treated with 100 mg and 2.48 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 regimens of either abrocitinib 100 mg or 200 mg, including the long-term extension study, the rate of PE was 0.21 per 100 patient-years for 200 mg and 0.05 per 100 patient-years for 100 mg. The rate of DVT was 0.06 per 100 patient-years in the 200 mg group and 0.05 per 100 patient-years in the 100 mg group (see section 4.4).

Thrombocytopenia
In placebo-controlled studies, for up to 16 weeks, treatment was associated with a dose-related decrease in platelet count. Maximum effects on platelets were observed within 4 weeks, after which the platelet count returned towards baseline despite continued therapy. Confirmed platelet counts of $< 50 \times 10^3/mm^3$ were reported in 0.1% of patients exposed to 200 mg, and in 0 patients treated with 100 mg or placebo. Among all patients treated with clinical studies with consistent dosing regimens of either abrocitinib 100 mg or 200 mg, including the long-term extension study, the rate of confirmed platelet counts of $< 50 \times 10^3/mm^3$ was 0.15 per 100 patients-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 abrocitinib 100 mg or 200 mg, including the long-term extension, the rate of confirmed ALC $< 0.5 \times 10^3/mm^3$ was 0.34 per 100 patient-years for 200 mg and 0.05 per 100 patient-years for 100 mg, the highest rate was observed in patients 65 years of age and older (see section 4.4).

Neutropenia
Among all patients treated in clinical studies with consistent dosing regimens of either abrocitinib 100 mg or 200 mg, including the long-term extension study, the incidence rate of confirmed ANC $< 1 \times 10^3/mm^3$ was 0.03 per 100 patient-years for 200 mg and 0 per 100 patient-years for 100 mg.

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

Creatine phosphokinase elevations (CPK)
In placebo-controlled studies, for up to 16 weeks, significant increases in CPK values ($> 5 \times$ ULN) occurred in 1.8% of patients treated with placebo, 1.8% of patients treated with 100 mg and 3.8% of patients treated with 200 mg of abrocitinib, respectively. Most elevations were transient and none led to discontinuation.

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

Paediatric population

A total of 635 adolescent patients (12 to less than 18 years of age) were treated with abrocitinib in clinical studies in atopic dermatitis representing 1 326.1 patient-years of exposure. The safety profile observed in adolescents in atopic dermatitis clinical studies was similar to that of the adult population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

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

Pharmacodynamic effects

Clinical biomarkers
Treatment with abrocitinib was associated with dose-dependent reduction in serum biomarkers of inflammation in atopic dermatitis [interleukin-31 (IL-31), interleukin-22 (IL-22), eosinophil count, and thymus and activation-regulated chemokine (TARC)], JAK1 signalling [natural killer (NK) cell

count and interferon gamma-induced protein 10 (IP-10)] or both [high sensitivity C-reactive protein (hsCRP)]. These changes were reversible after treatment discontinuation.

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

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

Clinical efficacy and safety

The efficacy and safety of abrocitinib as monotherapy and in combination with background medicated topical therapies over 12-16 weeks were evaluated in 1 616 patients in 3 pivotal Phase 3 randomised, double-blind, placebo-controlled studies (MONO-1, MONO-2, and COMPARE). In addition, the efficacy and safety of abrocitinib in monotherapy over 52 weeks (with the option of rescue treatment in flaring patients) was evaluated in 1 233 patients in a Phase 3 induction, randomised withdrawal, double-blind, placebo-controlled study (REGIMEN). The patients in these 4 studies were 12 years of age and older with moderate-to-severe atopic dermatitis as defined by Investigator's Global Assessment (IGA) score ≥ 3, Eczema Area and Severity Index (EASI) score ≥ 16, BSA involvement ≥ 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. A total of 134 patients 65 years of age and older were enrolled in these studies. In these studies, 32.2% to 40.8% had a baseline IGA of 4 (severe atopic dermatitis), and 41.4% to 59.5% of patients had received prior systemic treatment for atopic dermatitis. The baseline mean EASI score ranged from 28.5 to 30.9, the baseline PP-NRS ranged from 7.0 to 7.3 and the baseline Dermatology Life Quality Index (DLQI) ranged from 14.4 to 16.0.

Clinical response

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

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

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

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

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

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

	MONO-1[d]			**MONO-2[d]**		
	Week 12			**Week 12**		
	Abrocitinib monotherapy			**Abrocitinib 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[e] (35.9, 51.7)	23.7[e] (17.0, 30.4)	7.9 (1.8, 14.0)	38.1[e] (30.4, 45.7)	28.4[e] (21.3, 35.5)	9.1 (2.7, 15.5)
EASI-75[b]	62.7[e] (55.1, 70.4)	39.7[e] (32.1, 47.4)	11.8 (4.6, 19.1)	61.0[e] (53.3, 68.7)	44.5[e] (36.7, 52.3)	10.4 (3.6, 17.2)
PP-NRS4[c]	57.2[e] (48.8, 65.6)	37.7[e] (29.2, 46.3)	15.3 (6.6, 24.0)	55.3[e] (47.2, 63.5)	45.2[e] (37.1, 53.3)	11.5 (4.1, 19.0)

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

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. Abrocitinib used as monotherapy.
e. Statistically significant with adjustment for multiplicity versus placebo.

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

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

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

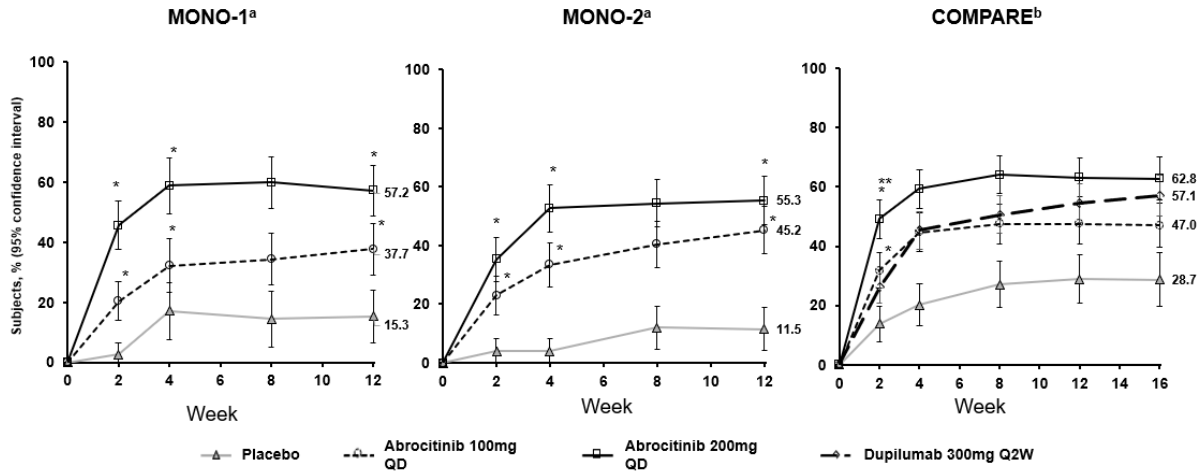
	COMPARE[d]						
	Week 12				Week 16		
	Abrocitinib + topicals		PBO + topicals N=131	DUP + topicals N=243	Abrocitinib + topicals		PBO + topicals N=131	DUP + topicals N=243
	200 mg QD N=226	100 mg QD N=238			200 mg QD N=226	100 mg QD N=238		

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

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. Abrocitinib used in combination with topical therapy.
e. Statistically significant with adjustment for multiplicity versus placebo.

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

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



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

a. Abrocitinib used as monotherapy.
b. Abrocitinib used in combination with medicated topical therapy.
* Statistically significant with adjustment for multiplicity versus placebo.
** Statistically significant with adjustment for multiplicity versus dupilumab.

Health-related outcomes

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

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

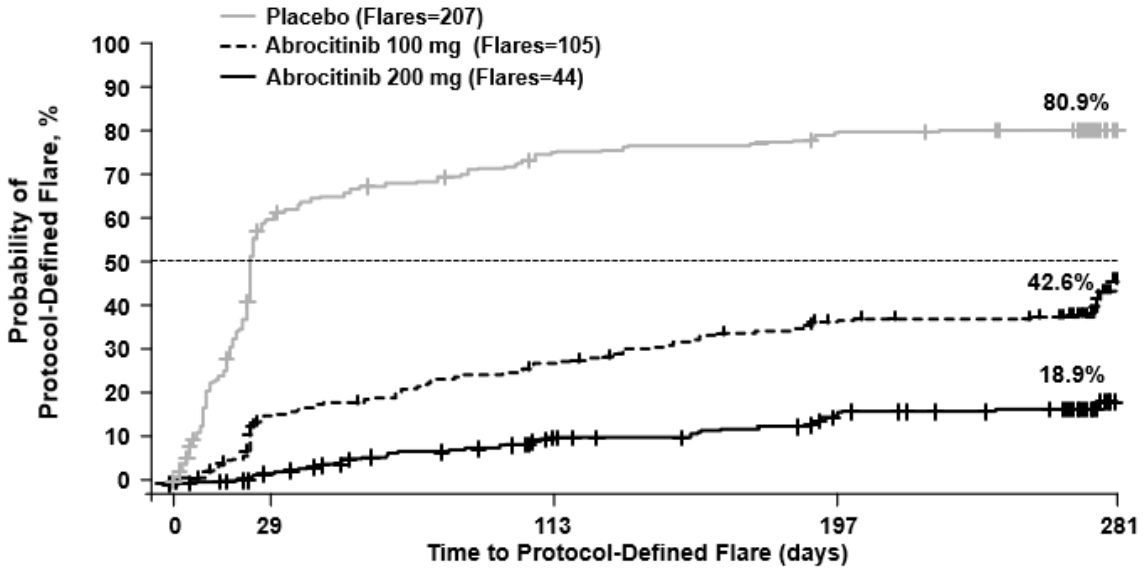
	Monotherapy						Combination therapy		
	MONO-1			MONO-2			COMPARE		
	200 mg QD	100 mg QD	PBO	200 mg QD	100 mg QD	PBO	200 mg QD + topicals	100 mg QD + topicals	PBO + topicals
N	**154**	**156**	**77**	**155**	**158**	**78**	**226**	**238**	**131**
SCORAD Sleep VAS, change from baseline (95% CI)	-3.7* (-4.2,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

CI=confidence interval; DLQI=Dermatology Life Quality Index; HADS=Hospital Anxiety and Depression Scale; N=number of patients randomised; PBO=placebo; POEM=Patient-Oriented Eczema Measure; QD=once daily; SCORAD=SCORing for AD; VAS=visual analog scale.
*Statistically significant without adjusting for multiplicity

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

Continuous treatment (200 mg continuous) and induction-maintenance treatment (200 mg for 12 weeks followed by 100 mg) prevented flare with 81.1% and 57.4% probability, respectively, versus 19.1% among patients who withdrew treatment (randomised to placebo) after 12 weeks of induction. Three-hundred fifty-one (351) patients including 16.2% of 200 mg, 39.2% of 100 mg and 76.4% of placebo patients received rescue medication of 200 mg abrocitinib in combination with topical therapy.

Figure 2. Time to protocol-defined flare



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

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

Among patients who achieved response after 12 weeks of treatment and entered EXTEND, the majority of patients maintained their response at Week 96 of cumulative treatment for both doses of abrocitinib [64% and 72% for IGA (0 or 1) response, 87% and 90% for EASI-75, and 75% and 80% for PP-NRS4 with 100 mg once daily and 200 mg once daily, respectively].

Among patients who did not achieve response after 12 weeks of treatment and entered EXTEND, a proportion of patients achieved late-onset response by Week 24 (from baseline) of continued treatment with abrocitinib [25% and 29% for IGA (0 or 1) response, and 50% and 57% for EASI-75 with 100 mg once daily and 200 mg once daily, respectively]. Patients who achieved partial response at Week 12 were more likely than those with no response at Week 12 to achieve treatment benefit at Week 24.

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

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with abrocitinib in one or more subsets of the paediatric population in the treatment of atopic dermatitis (see section 4.2 for information on paediatric use).

The efficacy and safety of 12 weeks of abrocitinib monotherapy were 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 of abrocitinib monotherapy over 52 weeks (with the option of rescue treatment for flaring patients) were also evaluated in an open-label induction, randomised withdrawal study (REGIMEN), which included 246 patients who were 12 to less than 18 years of age. In these studies, the results in the adolescent subgroup were consistent with the results in the overall study population.

The efficacy and safety of 12 weeks of abrocitinib in combination with background medicated topical therapy were evaluated in the Phase 3 randomised, double-blind, placebo-controlled study TEEN. The study included 287 patients who were 12 to less than 18 years of age with moderate-to-severe atopic dermatitis as defined by IGA score ≥ 3, EASI score ≥ 16, BSA involvement ≥ 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%.

Results of 12-week abrocitinib treatment in adolescents in pooled MONO-1 and MONO-2, and the TEEN study are shown in Table 6.

Table 6. Adolescent efficacy results at Week 12 in pooled MONO-1 and MONO-2, and in TEEN

	Pooled MONO-1 and MONO-2			**TEEN[d]**		
	Abrocitinib 200 mg QD	**Abrocitinib 100 mg QD**	**Placebo**	**Abrocitinib 200 mg QD**	**Abrocitinib 100 mg QD**	**Placebo**
IGA 0 or 1[a]						
N	48	50	23	93	89	94
%	31.3	22.0	8.7	46.2[e]	41.6[e]	24.5
95% CI	(18.1, 44.4)	(10.5, 33.5)	(0.0, 20.2)	(36.1, 56.4)	(31.3, 51.8)	(15.8, 33.2)
EASI-75[b]						
N	48	50	23	93	89	94
%	56.3	44.0	8.7	72.0[e]	68.5[e]	41.5
95% CI	(42.2, 70.3)	(30.2, 57.8)	(0.0, 20.2)	(62.9, 81.2)	(58.9, 78.2)	(31.5, 51.4)
PP-NRS4[c]						
N	36	42	22	74	76	84
%	61.1	28.6	9.1	55.4[e]	52.6	29.8
95% CI	(45.2, 77.0)	(14.9, 42.2)	(0.0, 21.1)	(44.1, 66.7)	(41.4, 63.9)	(20.0, 39.5)

Abbreviations: CI=confidence interval; EASI=Eczema Area and Severity Index; IGA=Investigator Global Assessment; N=number of evaluable patients; 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. Abrocitinib used in combination with medicated topical therapy.
e. Statistically significant with adjustment for multiplicity versus placebo.

Among adolescent patients who achieved response after 12 weeks of treatment and entered long-term extension study EXTEND, the majority of patients maintained their response at Week 96 of cumulative treatment for both doses of abrocitinib [62% and 78% for IGA (0 or 1) response, 89% and 93% for EASI-75, and 77% and 76% for PP-NRS4 with 100 mg and 200 mg once daily, respectively].

Among adolescent 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 both doses of abrocitinib [34% and 28% for IGA (0 or 1) response, and 41% and 55% for EASI-75 with 100 mg and 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 up to 200 mg. Co-administration of abrocitinib with a high-fat meal had no clinically relevant effect on abrocitinib exposures (AUC and C_{max} increased by approximately 26% and 29%, respectively, and T_{max} was prolonged by 2 hours). In clinical studies, abrocitinib was administered without regard to food (see section 4.2).

Distribution

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

Biotransformation

The *in vitro* metabolism of abrocitinib is mediated by multiple CYP enzymes, CYP2C19 (~53%), CYP2C9 (~30%), CYP3A4 (~11%) and CYP2B6 (~6%). In a human radiolabelled study, abrocitinib was the most prevalent circulating species, with mainly 3 polar mono-hydroxylated metabolites identified as M1 (3-hydroxypropyl), M2 (2-hydroxypropyl) and M4 (pyrrolidinone pyrimidine). At steady state, M2 and M4 are major metabolites and M1 is a minor metabolite. Of the 3 metabolites in circulation, M1 and M2 have similar JAK inhibitory profiles as abrocitinib, while M4 was pharmacologically inactive. The pharmacologic activity of abrocitinib is attributable to the unbound exposures of parent molecule (~60%) as well as M1 (~10%) and M2 (~30%) in systemic circulation. The sum of unbound exposures of abrocitinib, M1 and M2, each expressed in molar units and adjusted for relative potencies, is referred to as the abrocitinib active moiety.

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

Elimination

The elimination half-life of abrocitinib is about 5 hours. Abrocitinib is eliminated primarily by metabolic clearance mechanisms, with less than 1% of the dose excreted in urine as unchanged active substance. The metabolites of abrocitinib, M1, M2 and M4 are excreted predominantly in urine, and are substrates of OAT3 transporter.

Special populations

Body weight, gender, genotype, race and age
Body weight, gender, CYP2C19/2C9 genotype, race and age did not have a clinically meaningful effect on abrocitinib exposure (see section 4.2).

Adolescents (≥ 12 to <18 years)
Based on population pharmacokinetic analysis, there was no clinically relevant difference in mean abrocitinib steady-state exposures in adolescent patients compared to adults at their typical body weights.

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

Renal impairment

In a renal impairment study, patients with severe (eGFR < 30 mL/min) and moderate (eGFR 30 to< 60 mL/min) renal impairment had approximately 191% and 110% increase in active moiety AUC_{inf}, respectively, compared to patients with normal renal function (eGFR ≥ 90 mL/min) (see section 4.2*).* Pharmacokinetics of abrocitinib have not been determined in patients with mild renal impairment, however, based on the results observed in other groups, an increase of up to 70% in active moiety exposure is expected in patients with mild renal impairment (eGFR 60 to< 90 mL/min). The increase of up to 70% is not clinically meaningful as the efficacy and safety of abrocitinib in atopic dermatitis patients with mild renal impairment (n=756) was comparable to the overall population in Phase 2 and 3 clinical studies. The eGFR in individual patients was estimated using Modification of Diet in Renal Disease (MDRD) formula.

Abrocitinib has not been studied in patients with ESRD on renal replacement therapy (see section 4.2). In Phase 3 clinical studies, abrocitinib was not evaluated in patients with atopic dermatitis with baseline creatinine clearance values less than 40 mL/min.

Hepatic impairment

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

5.3 Preclinical safety data

General toxicity

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

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

MRHD of 200 mg) or in any of the toxicity studies in cynomolgus monkeys (comparable to human age of ≥ 8 years; up to 30 times the human AUC at the MRHD of 200 mg).

Genotoxicity

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

Carcinogenicity

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

Reproductive and developmental toxicity

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

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

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

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

Administration of abrocitinib to juvenile rats 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 at exposures ≥ 0.8 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 finding.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E460i)
Calcium hydrogen phosphate anhydrous (E341ii)
Sodium starch glycolate
Magnesium stearate (E470b)

Film-coat

Hypromellose (E464)
Titanium dioxide (E171)
Lactose monohydrate
Macrogol (E1521)
Triacetin (E1518)
Iron red oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Cibinqo 50 mg film-coated tablets

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

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

Cibinqo 100 mg film-coated tablets

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

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

Cibinqo 200 mg film-coated tablets

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

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

Cibinqo 50 mg film-coated tablets

EU/1/21/1593/001
EU/1/21/1593/002
EU/1/21/1593/003
EU/1/21/1593/004
EU/1/21/1593/005

Cibinqo 100 mg film-coated tablets

EU/1/21/1593/006
EU/1/21/1593/007
EU/1/21/1593/008
EU/1/21/1593/009
EU/1/21/1593/010

Cibinqo 200 mg film-coated tablets

EU/1/21/1593/011
EU/1/21/1593/012
EU/1/21/1593/013
EU/1/21/1593/014
EU/1/21/1593/015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 December 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pfizer Manufacturing Deutschland GmbH
Mooswaldallee 1
79108 Freiburg Im Breisgau
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of abrocitinib in each Member State the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing awareness about the safety concerns of the product, including, infections (including herpes zoster and serious and opportunistic infections), venous thromboembolism (VTE), malignancy, major adverse cardiovascular event (MACE), and embryo-foetal toxicity following exposure in utero.

The MAH shall ensure that in each Member State where abrocitinib is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense or use abrocitinib have access to/are provided with the following educational package:

The physician educational material should contain:

- The Summary of Product Characteristics
- Package leaflet
- Prescriber Brochure
- Patient card (PC)

The Prescriber Brochure shall contain the following key elements:

- Include a section about abrocitinib which describes the indication and posology.
- Language for Healthcare Professionals (HCPs) to inform patients of the importance of the PC.
- Use in patients aged 65 years and older
  - Language to reinforce risks in these patients and use of 100 mg dose
- *Infections (including herpes zoster and serious and opportunistic infections)*
  - Describe that Cibinqo must not be used in patients with active serious systemic infections.
  - Language on the risk of infections during treatment with Cibinqo.
  - Details on how to reduce the risk of infection with specific clinical measures (what laboratory parameters should be used to initiate Cibinqo, screening for TB, screening for hepatitis B and hepatitis C, getting patients immunised as per local guidelines, and temporary interruption of Cibinqo if an infection is not responding to standard therapy until the infection resolves).
  - Language stating the use of live, attenuated vaccines should be avoided during or immediately prior to treatment along with examples of live, attenuated vaccines.
  - Language recommending that risk factors for infections should be considered when prescribing abrocitinib, including elderly age and diabetes.
- *VTE*
  - Language describing the risk of VTE during treatment with Cibinqo.
  - Examples of risk factors which may put a patient at higher risk for VTE and in whom caution is needed when using abrocitinib.
  - Language that patients should be periodically re-evaluated for changes in VTE risk.
  - Language on the response if clinical features of VTE occur including prompt evaluation and the need for discontinuation of Cibinqo.
- *Malignancy*
  - Language describing that in patients at high risk for malignancy abrocitinib should only be used if no suitable treatment alternatives are available, with examples of who may be at high risk.
  - Reminder about the need for periodic skin examination for patients.
- *MACE*
  - Language describing that in patients at high risk for MACE abrocitinib should only be used if no suitable treatment alternatives are available, with examples of who may be at high risk.
  - Language that lipids should be monitored prior to initiation, after 4 weeks of therapy and thereafter according to clinical guidelines. Lipids should be managed according to clinical guidelines.
- *Embryo-foetal toxicity following exposure in utero*
  - Language describing that there are no or limited data on the use of Cibinqo in pregnant women.
  - Details on how to reduce the risk of exposure during pregnancy for women of childbearing potential based on the following: Cibinqo is contraindicated during pregnancy, women of childbearing potential should be advised to use effective contraception both during treatment and for 1 month after cessation of Cibinqo oral

administration, and to advise patients to inform their HCP immediately if they think they could be pregnant or if pregnancy is confirmed.

The patient information pack should contain:

- Package leaflet
- Patient card

- **The patient card** shall contain the following key messages:
  - Contact details of the Cibinqo prescriber.
  - Language that the PC should be carried by the patient at any time and to share it with HCPs involved in their care (i.e. non-Cibinqo prescribers, emergency room HCPs, etc.).
  - Language describing Cibinqo (i.e. what it is and what it is used for).
  - Risk of infections:
    - Description of signs/symptoms of infections the patient needs to be aware of, so that they can seek attention from their HCP:
    - Language to advise patients and their HCPs about the risk of live vaccinations when given immediately before and during Cibinqo therapy with examples of live vaccines.
  - Risk of blood clots in veins or lungs:
    - Description of signs/symptoms of blood clots in veins (deep venous thrombosis) or lungs (pulmonary embolism) which the patient needs to be aware of, so that they can seek immediate attention from an HCP.
  - Risk of heart disease:
    - Describe signs/symptoms of heart disease that the patient needs to be aware of, so that they can seek attention from their HCP.
  - Reminder of the risk of cancer. Regarding skin cancer reminder to let their doctor know if they notice any new growth on the skin.
  - Description of targeted risks for awareness by the patient and for HCPs involved in their care including:
    - The need for laboratory monitoring, including for high cholesterol.
    - A reminder to use contraception, that Cibinqo is contraindicated during pregnancy, and to notify their HCPs if they become pregnant while taking Cibinqo.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTER PACK AND BOTTLE LABEL FOR 50 MG

1. NAME OF THE MEDICINAL PRODUCT

Cibinqo 50 mg film-coated tablets
abrocitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg abrocitinib.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

Blister carton
14 film-coated tablets
28 film-coated tablets
91 film-coated tablets

Bottle
14 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Do not split, crush or chew.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBERS

Blister carton
EU/1/21/1593/003 14 film-coated tablets
EU/1/21/1593/004 28 film-coated tablets
EU/1/21/1593/005 91 film-coated tablets

Bottle
EU/1/21/1593/001 14 film-coated tablets
EU/1/21/1593/002 30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cibinqo 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS FOR 50 MG TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Cibinqo 50 mg film-coated tablets
abrocitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA holder logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon., Tue., Wed., Thu., Fri., Sat., Sun.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTERS PACK AND BOTTLE LABEL FOR 100 MG

1. NAME OF THE MEDICINAL PRODUCT

Cibinqo 100 mg film-coated tablets
abrocitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg abrocitinib.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

Blister carton
14 film-coated tablets
28 film-coated tablets
91 film-coated tablets

Bottle
14 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Do not split, crush or chew.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBERS

Blister carton
EU/1/21/1593/008 14 film-coated tablets
EU/1/21/1593/009 28 film-coated tablets
EU/1/21/1593/010 91 film-coated tablets

Bottle
EU/1/21/1593/006 14 film-coated tablets
EU/1/21/1593/007 30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cibinqo 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS FOR 100 MG TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Cibinqo 100 mg film-coated tablets
abrocitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA holder logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon., Tue., Wed., Thu., Fri., Sat., Sun.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTER PACK AND BOTTLE LABEL FOR 200 MG

1. NAME OF THE MEDICINAL PRODUCT

Cibinqo 200 mg film-coated tablets
abrocitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg abrocitinib.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

Blister carton
14 film-coated tablets
28 film-coated tablets
91 film-coated tablets

Bottle
14 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Do not split, crush or chew.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBERS

Blister carton
EU/1/21/1593/013 14 film-coated tablets
EU/1/21/1593/014 28 film-coated tablets
EU/1/21/1593/015 91 film-coated tablets

Bottle
EU/1/21/1593/011 14 film-coated tablets
EU/1/21/1593/012 30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cibinqo 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS FOR 200 MG TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Cibinqo 200 mg film-coated tablets
abrocitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA holder logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon., Tue., Wed., Thu., Fri., Sat., Sun.

B. PACKAGE LEAFLET

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.

In addition to this leaflet, your doctor will give you a patient card, which contains important safety information that you need to be aware of. Keep this patient card with you.

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 and adolescents 12 years and older 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, 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. If you have diabetes or are aged 65 years or older you may have an increased chance of getting infections.
- 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 ever had hepatitis B or hepatitis C.
- have recently had or plan to have a vaccination (immunisation) - this is because certain vaccines (live 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, if you use hormonal contraceptives\hormonal replacement therapy, if a coagulation defect is identified in you or your close relatives). 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 discoloration in the leg or arm as these can be signs of blood clots in the veins.
- have, or had heart problems because your doctor will discuss with you if Cibinqo is appropriate for you.
- have or have had cancer, smoke or have smoked in the past, because 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.

<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 12 years because the safety and benefits of Cibinqo are not yet 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.
- depression (such as citalopram, clobazam or escitalopram), as Cibinqo may increase their effects.

- neurofibromatosis type I (such as selumetinib), as Cibinqo may increase its effects.
- 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 decrease its effects.
- asthma, rheumatoid arthritis, or atopic dermatitis (such as biologic antibody therapies, medicines that control the body's immune response such as ciclosporin, other Janus kinase inhibitors, such as baricitinib, upadacitinib), as they may increase the risk of side 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 rifampicin), 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.

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'.

Elderly
Patients aged 65 years and older may be at increased risk of infections, heart attack and some types of cancer. Your doctor may decide that Cibinqo is not suitable for you.

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.

The recommended starting dose for adults and adolescents (12 years to 17 years of age) weighing at least 59 kg, is 100 mg or 200 mg once a day as prescribed by your doctor. Your doctor may increase or decrease your dose depending on how well the medicine is working.

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 or older.
- have a certain medical history or medical condition.
- are an adolescent (12 years to 17 years of age) weighing 25 kg-58 kg.

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 or medical condition, therefore you should always take this medicine exactly as your doctor has told you.

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
- Vomiting
- Stomach pain
- Headache
- Dizziness
- 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 platelet count shown by blood test
- Low white blood cell count shown by blood test (lymphocytes and neutrophils)
- 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. You can also report side effects directly via the national reporting system listed in Appendix V. 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, bottle and blister foil after EXP. The expiry date refers to the last day of that month.

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 (E460i), calcium hydrogen phosphate anhydrous (E341ii), sodium starch glycolate, magnesium stearate (E470b).
  Film-coat: hypromellose (E464), titanium dioxide (E171), lactose monohydrate, macrogol (E1521), 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, approximately 11 mm long and 5 mm wide oval tablets with “PFE” on one side and “ABR 50” on the other.

Cibinqo 100 mg tablets are pink, approximately 9 mm in diameter round tablets with “PFE” on one side and “ABR 100” on the other.

Cibinqo 200 mg tablets are pink, approximately 18 mm long and 8 mm wide oval tablets 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 or high-density polyethylene (HDPE) bottles with polypropylene closure. Each blister pack contains 14, 28 or 91 tablets. Each bottle contains 14 or 30 tablets.

Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for abrocitinib, the scientific conclusions of PRAC are as follows:

In view of available data on neutropenia, two cases reported with positive dechallenge and rechallenge as well as two additional reports with positive dechallenge together with clinical trial data and data from non-clinical trials where effect on neutrophil count was observed in rats, and potential class effect, the PRAC concluded that the product information of abrocitinib should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation

On the basis of the scientific conclusions for abrocitinib the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing abrocitinib is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation should be varied.