**PT. PFIZER INDONESIA**
**Local Product Document**

Generic Name: Abrocitinib
Trade Name: FREORLA
CDS Effective Date: June 04, 2021
Supersedes: NA

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FREORLA 50 mg film-coated tablets

Each film-coated tablet contains 50 mg abrocitinib

FREORLA 100 mg film-coated tablets

Each film-coated tablet contains 100 mg abrocitinib

FREORLA 200 mg film-coated tablets

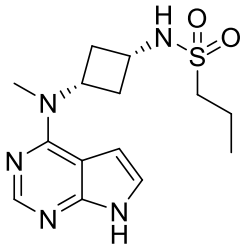
Each film-coated tablet contains 200 mg abrocitinib

Excipients with known effects

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

For a full list of excipients, see Section 6.1

Structure of abrocitinib:



## 3. PHARMACEUTICAL FORM

Film-coated tablet.

FREORLA 50 mg film-coated tablets
Pink, oval tablet 10.50 mm long and 4.75 mm wide, debossed with “PFE” on one side and “ABR 50” on the other.

FREORLA 100 mg film-coated tablets
Pink, round tablet 9.00 mm in diameter, debossed with “PFE” on one side and “ABR 100” on the other.

FREORLA 200 mg film-coated tablets
Pink, oval tablet 18.42 mm long and 8.00 mm wide debossed with “PFE” on one side and “ABR 200” on the other.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

FREORLA is indicated for the treatment of adult patients with age 18 years or older with moderate-to-severe atopic dermatitis, including the relief of pruritus, who have had an inadequate response to prescribed topical therapy or for whom these treatments are not advisable. FREORLA can be used with or without medicated topical therapies for atopic dermatitis.

### 4.2. Posology and method of administration

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

Posology

The recommended dose of FREORLA is 100 mg or 200 mg once daily, based on individual goal of therapy and potential risk for adverse reactions.

- A starting dose of 100 mg once daily is recommended for patients more than equal to 65 years of age. For other patients who may benefit from a starting dose of 100 mg (see Sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects).

- During treatment, the dose may be decreased or increased based on tolerability and efficacy. The lowest effective dose for maintenance should be considered. The maximum daily dose is 200 mg.

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

FREORLA should be taken orally once daily with or without food at approximately the same time each day.

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

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

*Laboratory monitoring*

**Table 1. Laboratory Measures and Monitoring Guidance**

| **Laboratory measure** | **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 hyperlipidemia. |

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

*Dose interruption*
If a patient develops a serious infection, sepsis or opportunistic infection, consider interruption of FREORLA until the infection is controlled should be considered (see Section 4.4).

Interruption of dosing may be needed for management of laboratory abnormalities as described in Table 2 (see Section 4.4).

*Drug-drug 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. Treatment is not recommended concomitantly with moderate or strong inducers of CYP2C19/CYP2C9 enzymes (e.g. rifampicin, apalutamide, efavirenz, enzalutamide, phenytoin).
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 less than 60 mL/min) renal impairment, the recommended dose of abrocitinib should be reduced by half to 100 mg or 50 mg once daily. In patients with severe (eGFR less than 30 mL/min) renal impairment, 50 mg once daily is the recommended starting dose. The maximum daily dose is 100 mg. The use of FREORLA 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. FREORLA has not been studied in patients with severe (Child Pugh C) hepatic impairment (see Section 5.2).

*Elderly population*
The recommended starting dose for patients aged 65 years or more is 100 mg once daily.
*Pediatric population*
FREORLA is not recommended for pediatric patients under 18 years of age. The safety and efficacy of FREORLA in pediatric patients under 12 years of age have not yet been established. No data are available.

Method of administration

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

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

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

**4.3. Contraindications**

- Hypersensitivity to the active substance or to any of the excipients listed.

- Active serious systemic infections, including tuberculosis (TB).
- Severe hepatic impairment.
- Pregnancy and breast-feeding.

**4.4. Special warnings and precautions for use**

Serious infections

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

Treatment must not be initiated in patients with an active, serious systemic infections.

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 FREORLA. A patient who develops a new infection during treatment with FREORLA should undergo prompt and complete diagnostic testing and appropriate antimicrobial therapy should be initiated. The patient should be closely monitored and FREORLA therapy should be interrupted if the patient is not responding to standard therapy.

*Tuberculosis*
Patients should be screened for tuberculosis (TB) before starting FREORLA therapy and consider yearly screening for patients in highly endemic areas for TB. FREORLA should not be given to patients with active TB. 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 FREORLA.

*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 65 years of age and older and patients with severe atopic dermatitis at baseline. 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 with FREORLA. Patients with evidence of active hepatitis B or hepatitis C (positive hepatitis C PCR) infection were excluded from clinical studies (see Section 5.2). Patients who were hepatitis B surface antigen negative, hepatitis B core antibody positive, and hepatitis B surface antibody positive had testing for hepatitis B virus (HBV) DNA.

Patients who had HBV DNA above the lower limit of quantification (LLQ) were excluded. Patients who had HBV DNA negative or below LLQ could initiate treatment with FREORLA; 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. Avoid use of live, attenuated vaccines during or immediately prior to FREORLA therapy is not recommended. Prior to initiating FREORLA, it is recommended that patients be brought up to date with all immunizations, including prophylactic herpes zoster vaccinations, in agreement with current immunization guidelines.

Venous thromboembolism

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving Janus kinase (JAK) inhibitors including FREORLA (see Section 4.8). FREORLA should be used with caution in patients at high risk for DVT/PE. Risk factors that should be considered in determining the patient's risk for DVT/PE include older age, obesity, a medical history of DVT/PE, prothrombotic disorder, use of combined hormonal contraceptives or hormone replacement therapy, patients undergoing major surgery, or prolonged immobilization. If clinical features of DVT/PE occur, FREORLA treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.

Malignancy (including non-melanoma skin cancers)

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

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

Hematologic 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 FREORLA should not be initiated in patients with a platelet count $<150 \times 10^3/mm^3$, an ALC $<0.5 \times 10^3/mm^3$, an ANC $<1 \times 10^3/mm^3$ or who have a hemoglobin value <8 g/dL (see Section 4.2). Platelet count and ALC should be monitored 4 weeks after initiation of therapy with FREORLA and thereafter according to routine patient management.

Lipids

Dose-dependent increase in blood lipid parameters were reported in patients treated with FREORLA (see Section 4.8). Lipid parameters should be assessed approximately 4 weeks following initiation of FREORLA therapy and thereafter patients should be managed according to clinical guidelines for hyperlipidemia. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined. Patients with abnormal lipid parameters should be further monitored and managed according to clinical guidelines, due to the known cardiovascular risks associated with hyperlipidaemia. In patients with a high burden of cardiovascular risk factors, the risks and benefits of abrocitinib compared to that of other available therapies for atopic dermatitis should be considered. If abrocitinib is chosen, interventions to manage lipid concentrations should be implemented according to clinical guidelines.

**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.

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

**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 FREORLA

Abrocitinib is metabolized 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.

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

*Coadministration with CYP2C19/CYP2C9 inducers*
Administration of FREORLA 200 mg after multiple dosing with rifampin, a strong inducer of CYP enzymes, resulted in reduction of abrocitinib active moiety exposures by approximately 56%.

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

*Co-administration with products which increase gastric pH*
The effect of elevating gastric pH with antacids, H2-receptor antagonists (famotidine), or proton pump inhibitors (omeprazole) on the pharmacokinetics of abrocitinib has not been studied and may reduce the absorption of abrocitinib due to the low solubility of abrocitinib at pH above 4.

Potential for FREORLA to affect pharmacokinetics of other medicines

In vitro, abrocitinib or its metabolites were not significant inhibitors or inducers of CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) or of uridine diphosphate-glucuronyltransferases (UGTs) (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7). In vitro, abrocitinib is an inhibitor of P-glycoprotein (P-gp), organic anion transporter (OAT)3, organic cation transporter (OCT)1, multidrug and toxin compound extrusion protein (MATE)1/2K and breast cancer resistance protein (BCRP) but is not an inhibitor of organic anion transporting polypeptide (OATP)1B1/1B3, bile salt export pump (BSEP), OAT1 or OCT2 at clinically meaningful concentrations. The metabolites do not change the transporter inhibition risk compared to abrocitinib.
No clinically significant effects of FREORLA were observed in drug interaction studies with oral contraceptives (e.g., ethinyl estradiol/levonorgestrel), or with substrates of BCRP and OAT3 (e.g., rosuvastatin), MATE1/2K (e.g., metformin) and CYP3A4 (e.g., midazolam).
Coadministration of dabigatran etexilate (a P-gp substrate), with a single dose of FREORLA 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 inducer of CYP2B6 and CYP1A2, and an inducer and inhibitor of CYP2C19 enzymes. Pharmacokinetic interaction studies have not been performed with subtrates of CYP2B6, CYP1A2 and CYP2C19. The exposures of medicinal products metabolized by CYP2B6 (e.g., bupropion, efavirenz) and CYP1A2 (e.g., alosetron, duloxetine, ramelteon, tizanidine) may be decreased and of those metabolized by CYP2C19 (e.g., S-mephenytoin) may be increased initially and then decreased, when used concomitantly with abrocitinib.

## 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 FREORLA. Consider pregnancy planning and prevention for females of reproductive potential.

Pregnancy

The limited human data on use of FREORLA in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage. In embryo-fetal development studies, oral administration of FREORLA to pregnant rats during organogenesis resulted in fetotoxicity at exposures equal to 17 times the unbound AUC at the maximum recommended human dose (MRHD) of 200 mg once daily. In embryo-fetal development studies, oral administration of FREORLA to pregnant rabbits did not result in fetotoxicity at exposures equal to 4 times the unbound AUC at the MRHD of 200 mg. In a pre- and postnatal development study in pregnant rats, FREORLA oral administration during gestation and through lactation resulted in lower postnatal survival and lower offspring body weights at exposures greater than or equal to 11 times the unbound AUC at the MRHD of 200 mg once daily (see Section 5.3). FREORLA is contraindicated during pregnancy.

Breastfeeding

There are no data on the presence of FREORLA in human milk, the effects on the breastfed infant, or the effects on milk production. FREORLA was secreted in milk of lactating rats. A risk to newborns/infants cannot be excluded and FREORLA is contraindicated during breast-feeding.

Fertility

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

## 4.7. Effects on ability to drive and use machines

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

## 4.8. Undesirable effects

Summary of safety profile

The most commonly reported adverse reactions (ARs) occurring in ⩾2% of patients treated with FREORLA in placebo-controlled studies were nausea (10.3%), headache (6.8%), herpes simplex (3.8%), acne (3.2%), blood creatine phosphokinase increased (2.6%), dizziness (2.3%), and

vomiting (2.3%). The most frequent serious adverse reactions in atopic dermatitis patients were infections (see Section 4.4).

Tabulated list of adverse reactions

A total of 2856 patients were treated with FREORLA in clinical studies in atopic dermatitis representing 1614 patient-years of exposure. There were 606 patients with more than 1 year of exposure to FREORLA. Four placebo-controlled studies were integrated (608 patients on 100 mg once daily, 590 patients on 200 mg once daily and 342 patients on placebo) to evaluate the safety of FREORLA in comparison to placebo for up to 16 weeks.

**Table 2. Adverse reactions for FREORLA**

| **System Organ Class** | **Very Common ≥1/10** | **Common ≥1/100 to <1/10** | **Uncommon ⩾1/1,000 to <1/100** |
|---|---|---|---|
| Infections and infestations | | Herpes simplex[a] | Herpes zoster[b]<br>Pneumonia |
| Blood and lymphatic system disorders | | | Thrombocytopenia<br>Lymphopenia |
| Metabolism and nutrition disorders | | | Hyperlipidaemia[c] |
| Nervous system disorders | | Headache<br>Dizziness | |
| Vascular disorders | | | Venous thromboembolism[d] |
| Gastrointestinal disorders | Nausea | Vomiting<br>Abdominal pain upper | |
| Skin and subcutaneous tissue disorders | | Acne | |
| Investigations | | Blood creatine phosphokinase increased | |

a. Herpes simplex includes oral herpes, ophthalmic herpes simplex, genital herpes, and herpes dermatitis.
b. Herpes zoster includes ophthalmic herpes zoster.
c. Hyperlipidaemia included dyslipidaemia and hypercholesterolaemia.
d. Venous thromboembolism includes pulmonary embolism and deep vein thrombosis.

Description of selected adverse reactions

*Overall infections*
In placebo-controlled studies, for up to 16 weeks, overall infections have been reported in 26.3% of patients treated with placebo and in 35.2% and 34.6% of patients treated with FREORLA 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 (0.61 per 100 patient-years in the abrocitinib 100 mg group and 1.23 per 100 patient-years in the abrocitinib 200 mg group ), most of which were non-serious multidermatomal cutaneous infections. Among all patients treated in clinical studies with consistent dosing regimens of either abrocitinib 100 mg or 200 mg, including the long-term extension study, the incidence rate of herpes zoster in patients treated with abrocitinib 200 mg (4.83 per 100 patient-years) was higher than that of patients treated with 100 mg (2.39 per 100 patient-years). Incidence rates for herpes zoster were also higher for patients 65 years of age and older (HR 3.68), patients with a medical history of herpes zoster (HR 3.61), patients with severe atopic dermatitis at baseline (HR 1.28), and a confirmed ALC < $1.0 \times 10^3$ /$mm^3$ prior to the event of herpes zoster (HR 1.84).

*Serious infections*
In placebo-controlled studies, for up to 16 weeks, serious infections have been reported in 2 patients (2.31 per 100 patient-years) treated with placebo, 6 patients (3.80 per 100 patient-years) treated with FREORLA 100 mg, and 2 patients (1.28 per 100 patient-years) treated with FREORLA 200 mg. Among all patients treated with FREORLA, including the long-term extension study, serious infections were reported in 17 patients (2.65 per 100 patient-years) treated with FREORLA 100 mg and 24 patients (2.33 per 100 patient-years) treated with FREORLA 200 mg. The most commonly reported serious infections were herpes simplex, herpes zoster, and pneumonia (see Section 4.4).

*Opportunistic infections*
All observed opportunistic infections were cases of multidermatomal cutaneous herpes zoster. Among all patients treated with FREORLA, including the long-term extension study, opportunistic infections were reported in 3 patients (0.47 per 100 patient-years) treated with FREORLA 100 mg and 10 patients (0.97 per 100 patient-years) treated with FREORLA 200 mg. Most cases of opportunistic herpes zoster were mild or moderate.

*Venous thromboembolism*
Among all patients treated with FREORLA, including the long-term extension study, PE was reported in 3 patients (0.18 per 100 patient-years), all treated with FREORLA 200 mg. Events of

DVT were reported in 2 patients (0.09 per 100 patient-years) treated with FREORLA 200 mg (see Section 4.4).

*Thrombocytopenia*
In placebo-controlled studies, for up to 16 weeks, treatment with FREORLA 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 1 patient (0.1%) exposed to FREORLA 200 mg, 0 patients treated with FREORLA 100 mg or placebo. Among all patients exposed to FREORLA, including the long-term extension study, confirmed platelet counts of $<50 \times 10^3/mm^3$ were reported in 2 patients (0.1%), both treated with FREORLA 200 mg (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 2 patients (0.3%) treated with FREORLA 200 mg and 0 patients treated with FREORLA 100 mg or placebo. Both cases occurred in the first 4 weeks of exposure. Among all patients exposed to FREORLA, including the long-term extension, confirmed ALC $<0.5 \times 10^3/mm^3$ were reported in 4 patients (0.1%) treated with 200 mg of FREORLA and 0 patients treated with FREORLA 100 mg (see Section 4.4).

*Lipid elevations*
In placebo-controlled studies, for up to 16 weeks, there was a dose-related percent increase in low-density lipoprotein cholesterol (LDL-c), total cholesterol, and high-density lipoprotein cholesterol (HDL-c) relative to placebo at Week 4 which remained elevated through the final visit in the treatment period. There was no change in the LDL/HDL ratio or triglycerides. Events related to hyperlipidemia occurred in 1 patient (0.2%) exposed to FREORLA 100 mg, 7 patients (1.2%) exposed to FREORLA 200 mg and 0 patients exposed to placebo (see Section 4.4).

*Creatine phosphokinase elevations (CPK)*
In placebo-controlled studies, for up to 16 weeks, events of blood CPK increased were reported in 1.5% of patients treated with placebo, 2.3% and 2.9% of patients treated with 100 mg and 200 mg of FREORLA, respectively.[43] Most elevations were transient, and none led to discontinuation. In the clinical studies, there were no reported events of rhabdomyolysis.

*Nausea*
Nausea was most frequent in the first week of FREORLA therapy and generally resolved with continued therapy. The median duration of nausea was 15 days. Most of the cases were mild to moderate in severity.
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.

Pediatric population

The pharmacokinetics, safety and efficacy of FREORLA in pediatric patients under 12 years of age have not yet been established.

Of the 2856 patients with atopic dermatitis exposed to FREORLA, a total of 364 adolescents (12 to less than 18 years of age) were enrolled in FREORLA studies. The safety profile observed in adolescents in atopic dermatitis clinical studies was similar to that of the adult population. There were no adolescent patients who developed platelet counts $<75 \times 10^3/mm^3$ or absolute lymphocyte count $<0.5 \times 10^3/mm^3$.

Elderly population

A total of 145 patients 65 years of age and older were enrolled in FREORLA studies. The safety profile observed in elderly patients was similar to that of the adult population overall. A higher proportion of patients 65 years of age and older discontinued from clinical studies compared to younger patients. Among all patients exposed to FREORLA including the long-term extension study, confirmed ALC $<0.5 \times 10^3/mm^3$ occurred only in patients 65 years of age and older. A higher proportion of patients 65 years of age and older had platelet counts $<75 \times 10^3/mm^3$. The incidence rate of herpes zoster in patients 65 years of age and older treated with FREORLA (7.40 per 100 patient-years) was higher than that of patients 18 to less than 65 years of age (3.44 per 100 patient-years) and less than 18 years of age (2.12 per 100 patient-years). There is limited data in patients above 75 years of age.

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.

**4.9. Overdose**

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

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Mechanism of action

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

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

Pharmacodynamic effects

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

Clinical efficacy and safety

The efficacy and safety of FREORLA as monotherapy and in combination with background medicated topical therapies were evaluated in 3 pivotal randomized, double-blind, placebo-controlled studies (MONO-1, MONO-2, and COMPARE) in 1616 patients 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, body surface area (BSA) involvement ≥10%, and Peak Pruritus Numerical Rating Scale (PP-NRS) ≥4 at the baseline visit prior to randomization.

Patients in these studies were those who had inadequate response to previous topical medication, or were patients for whom topical treatments were medically inadvisable, or who had received systemic therapies including dupilumab. In each of the pivotal studies, over 40% of patients had

prior exposure to systemic therapy. In MONO-1 and MONO-2, 6% of the patients had received dupilumab, whereas prior use of dupilumab was not allowed in COMPARE.

Eligible patients from qualifying parent studies were able to enroll in the long-term extension study EXTEND, e.g., if they completed the full treatment period of the any of the pivotal qualifying parent studies.

MONO-1, MONO-2, and COMPARE assessed the co-primary endpoints of IGA and EASI-75 responses at Week 12. Key secondary endpoints in MONO-1 and MONO-2 included improvement of ≥4 points in the severity of PP-NRS (PP-NRS4) at Week 12 and change from baseline to Week 12 for the Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD). The PSAAD is an 11-item, self-reported instrument using a 24-hour recall period, designed to assess the severity of key symptoms and signs of atopic dermatitis including itching, pain, dryness, flaking, cracking, bumps, redness, discoloration, bleeding, fluid, and swelling. Key secondary endpoints in COMPARE were PP-NRS4 at Week 2 in addition to IGA response and EASI-75 at Week 16. The designs of the pivotal and long-term extension studies are summarized in Table 4.

**Table 3. Clinical study summary**

| **Study name (regimen type)**<br><br>**Treatment duration** | **Population (number of randomized patients)** | **Treatment arms** | **Primary and key secondary endpoints** |
|---|---|---|---|
| MONO-1 (monotherapy)<br><br>12 weeks | Adults and adolescents (387) | • FREORLA 200 mg QD<br>• FREORLA 100 mg QD<br>• Placebo | Co-primary<br>• IGA response[a] at Week 12<br>• EASI-75[b] at Week 12<br><br>Key secondary<br>• PP-NRS4[c] at Weeks 2, 4 and 12<br>• Change from baseline in PSAAD[d] at Week 12 |
| MONO-2 (monotherapy)<br><br>12 weeks | Adults and adolescents (391) | • FREORLA 200 mg QD<br>• FREORLA 100 mg QD<br>• Placebo | Co-primary<br>• IGA response at Week 12<br>• EASI-75 at Week 12<br><br>Key secondary<br>• PP-NRS4 at Weeks 2, 4 and 12<br>• Change from baseline in PSAAD at Week 12 |
| COMPARE (combination therapy) | Adults (838) | • FREORLA 200 mg QD<br>• FREORLA 100 mg QD<br>• Placebo | Co-primary<br>• IGA response at Week 12<br>• EASI-75 at Week 12 |

| | | | |
|---|---|---|---|
| 16 weeks | | • Dupilumab 300 mg Q2W SC[e]<br><br>All patients received background medicated topical therapy | Key secondary<br>• PP-NRS4 at Week 2<br>• IGA response at Week 16<br>• EASI-75 at Week 16 |
| EXTEND (long-term extension)<br><br>variable | Adults and adolescents (approximately 2300) | • FREORLA 200 mg QD<br>• FREORLA 100 mg QD | Primary<br>• Long-term safety |

Primary and key secondary endpoints were controlled for multiplicity.
Abbreviations: EASI=Eczema Area and Severity Index; IGA=Investigator Global Assessment; PP-NRS=Peak Pruritus Numerical Rating Scale; PSAAD=Pruritus and Symptoms Assessment for Atopic Dermatitis; QD=once daily; Q2W=once every 2 weeks; SC=subcutaneously.

a. IGA response was based on 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 was based on ⩾75% improvement in EASI from baseline.
c. PP-NRS4 response was based on an improvement of ⩾4 points in the severity of PP-NRS.
d. PSAAD ranges from 0 to 10 with higher scores indicating greater levels of atopic dermatitis symptom severity.
e. Dupilumab treatment in COMPARE: An initial dose of 600 mg on day 1, followed by 300 mg Q2W.

*Clinical response*

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

*Monotherapy studies*

In both pivotal monotherapy studies (MONO-1, MONO-2), the proportion of patients who achieved IGA and/or EASI-75 response was significantly higher in patients who received FREORLA 100 mg or 200 mg once daily compared with placebo at Week 12 (see Table 5).

A significantly higher proportion of patients who achieved PP-NRS4 (defined as an improvement of ≥4 points in the severity of PP-NRS) with FREORLA 100 mg or 200 mg once daily compared with placebo was observed as soon as Week 2 and persisting through Week 12. Higher proportions of patients achieved PP-NRS4 with FREORLA 100 mg or 200 mg once daily compared with placebo by Day 6 and Day 3 (2 days after the first dose), respectively (see Table 5).

**Table 4. Efficacy results of FREORLA monotherapy at Week 12**

| | **MONO-1** | | | **MONO-2** | | |
|---|---|---|---|---|---|---|
| | **ABR** | | | **ABR** | | |
| | **200 mg QD N=154** | **100 mg QD N=156** | **Placebo N=77** | **200 mg QD N=155** | **100 mg QD N=158** | **Placebo N=78** |
| | **% Responders (95% CI)** | | | | | |
| IGA 0 or 1[a] | 43.8[g] (35.9, 51.7) | 23.7[e] (17.0, 30.4) | 7.9 (1.8, 14.0) | 38.1[g] (30.4, 45.7) | 28.4[f] (21.3, 35.5) | 9.1 (2.7, 15.5) |
| EASI-50[b] | 75.8[k] (69.0, 82.6) | 57.7[k] (49.9, 65.4) | 22.4 (13.0, 31.7) | 79.9[k] (73.5, 86.2) | 68.4[k] (61.1, 75.7) | 19.5 (10.6, 28.3) |
| EASI-75[b] | 62.7[g] | 39.7[g] | 11.8 | 61.0[g] | 44.5[g] | 10.4 |

**Table 4. Efficacy results of FREORLA monotherapy at Week 12**

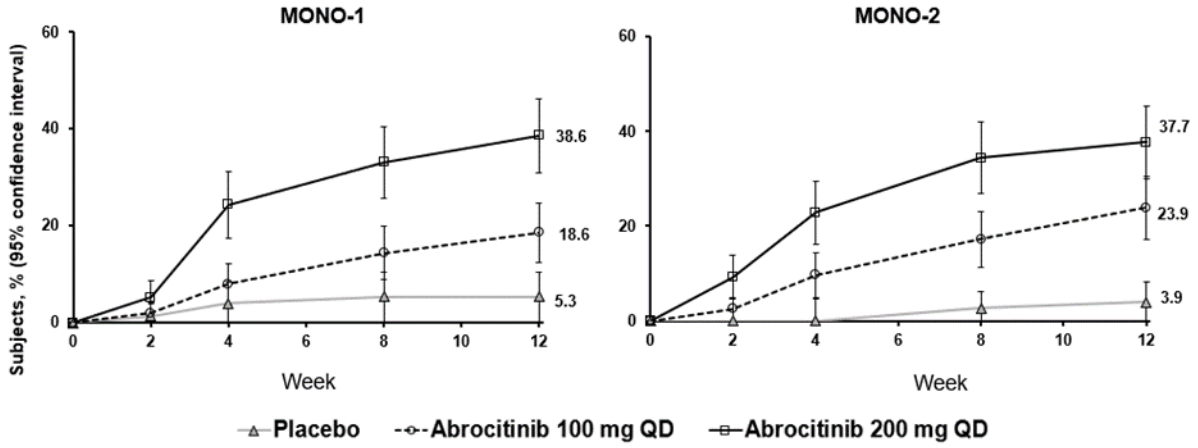
| | MONO-1 | | | MONO-2 | | |
|---|---|---|---|---|---|---|
| | ABR | | | ABR | | |
| | 200 mg QD N=154 | 100 mg QD N=156 | Placebo N=77 | 200 mg QD N=155 | 100 mg QD N=158 | Placebo N=78 |
| | (55.1, 70.4) | (32.1, 47.4) | (4.6, 19.1) | (53.3, 68.7) | (36.7, 52.3) | (3.6, 17.2) |
| EASI-90[b] | 38.6[k] (30.8, 46.3) | 18.6[i] (12.5, 24.7) | 5.3 (0.2, 10.3) | 37.7[k] (30.0, 45.3) | 23.9[k] (17.2, 30.6) | 3.9 (0.0, 8.2) |
| EASI-100[b] | 13.1[i] (7.7, 18.4) | 6.4[h] (2.6, 10.3) | 0 (0.0, 4.7) | 7.1[h] (3.1, 11.2) | 5.2[h] (1.7, 8.6) | 0 (0.0, 4.7) |
| PP-NRS4[c,d] | 57.2[g] (48.8, 65.6) | 37.7[f] (29.2, 46.3) | 15.3 (6.6, 24.0) | 55.3[g] (47.2, 63.5) | 45.2[g] (37.1, 53.3) | 11.5 (4.1, 19.0) |
| PP-NRS (0 or 1) | 35.4[k] (27.2, 43.6) | 21.1[i] (13.9, 28.4) | 3.2 (0.0, 7.5) | 32.4[k] (24.5, 40.2) | 21.3[i] (14.5, 28.0) | 5.5 (0.3, 10.7) |
| | % Change from baseline (95% CI) | | | | | |
| LSM EASI | -73.5[k] (-79.1, -68.0) | -57.5[k] (-63.1, -51.9) | -28.4 (-36.5, -20.3) | -73.3[k] (-79.7, -66.9) | -60.0[k] (-66.5, -53.6) | -28.6 (-38.4, -18.8) |
| LSM PP-NRS | -56.5[k] (-63.6, -49.5) | -39.5[i] (-46.7, -32.3) | -19.5 (-30.0, -9.0) | -56.9[k] (-64.0, -49.8) | -43.5[j] (-50.7, -36.3) | -20.8 (-31.6, -9.9) |
| LSM SCORAD | -55.1[k] (-60.1, -50.2) | -41.5[k] (-46.5, -36.5) | -21.6 (-28.7, -14.5) | -56.2[k] (-61.2, -51.1) | -45.8[k] (-50.9, -40.7) | -22.7 (-30.4, -15.1) |
| | Change from baseline (95% CI) | | | | | |
| LSM PSAAD | -3.2[g] (-3.6, -2.8) | -2.2[e] (-2.6, -1.9) | -1.1 (-1.7, -0.6) | -3.0[g] (-3.3, -2.7) | -2.4[g] (-2.8, -2.1) | -0.8 (-1.3, -0.3) |

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

a. IGA responders were patients with IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥ 2 points.
b. EASI-50, -75, -90 and -100 responders were patients with ≥50%, ≥75%, ≥90%, and ≥100% improvement, respectively in EASI, from baseline.
c. The proportion of PP-NRS4 responders was also significantly higher with FREORLA 200 mg and 100 mg once daily than placebo at Week 2, Week 4, and Week 8 in both MONO-1 and MONO-2.
d. PP-NRS4 responders were patients with ≥4-point improvement in PP-NRS from baseline.
e. Multiplicity-controlled p <0.01 versus placebo.
f. Multiplicity-controlled p <0.001 versus placebo.
g. Multiplicity-controlled p <0.0001 versus placebo.
h. Nominal p <0.05 versus placebo.
i. Nominal p <0.01 versus placebo.
j. Nominal p <0.001 versus placebo.
k. Nominal p <0.0001 versus placebo.

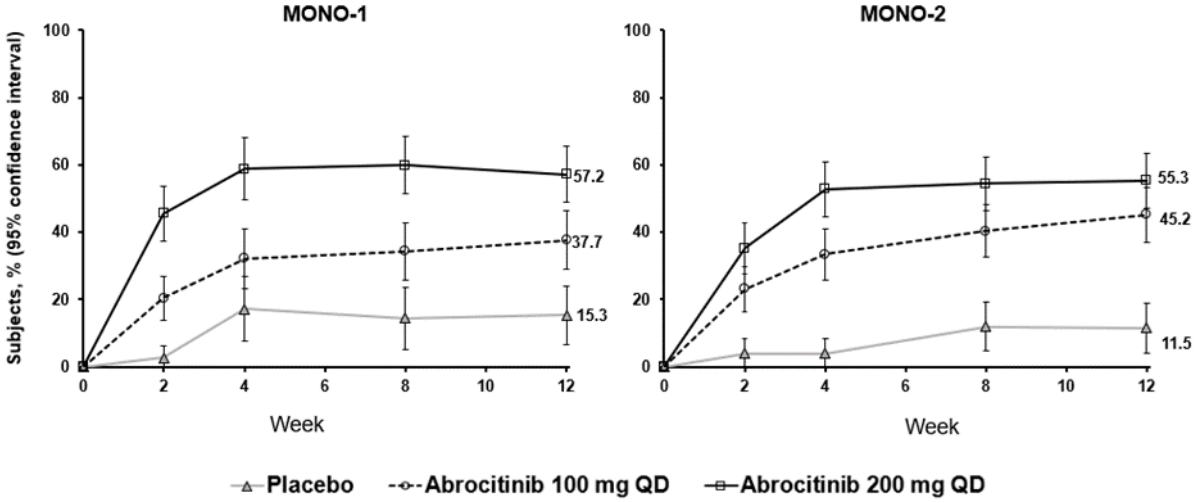
The proportion of patients who achieved EASI-90 or PP-NRS4 over time in studies MONO-1 and MONO-2 are shown in Figures 1 and 2.

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




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

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




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

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

*Combination therapy study*
In the pivotal combination therapy study (COMPARE), the proportion of patients who achieved IGA or EASI-75 response was significantly higher in patients who received FREORLA 100 mg or 200 mg once daily compared with placebo at Week 12 (see Table 6).

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

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

**Table 5. Efficacy results of FREORLA with concomitant topical therapy**

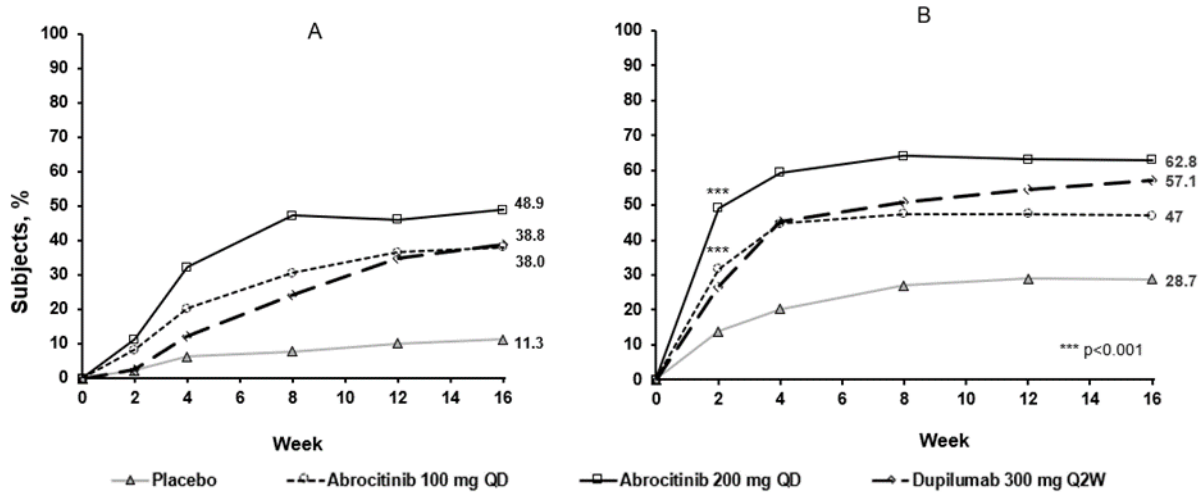
| | Week 2 | | | | Week 12 | | | | Week 16 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ABR | | | | ABR | | | | ABR | | | |
| | 200 mg N=226 | 100 mg N=238 | PBO N=131 | DUP N=243 | 200 mg N=226 | 100 mg N=238 | PBO N=131 | DUP N=243 | 200 mg N=226 | 100 mg N=238 | PBO N=131 | DUP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

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

a. IGA responders were patients with IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥ 2 points.
b. EASI-50, -75, -90 and -100 responders were patients with ≥50%, ≥75%, ≥90% and ≥100% improvement in EASI, respectively, from baseline.
c. PP-NRS4 responders were patients with ≥4-point improvement in PP-NRS from baseline.
d. Multiplicity-controlled p <0.001 vs. placebo
e. Multiplicity-controlled p <0.0001 vs. placebo
f. Multiplicity-controlled p <0.0001 vs. dupilumab. Statistical comparison between either abrocitinib dose and dupilumab was only performed on the proportion of patients achieving PP-NRS4 at Week 2.
g. Nominal p <0.05 vs. placebo
h. Nominal p <0.01 vs. placebo
i. Nominal p <0.001 vs. placebo
j. Nominal p <0.0001 vs. placebo

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

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




Abbreviations: EASI=Eczema Area and Severity Index; PP-NRS=Peak Pruritus Numerical Rating Scale; QD=once daily; Q2W=every 2 weeks.
EASI-90 was based on EASI ≥90% improvement from baseline.
PP-NRS4 response was based on achieving at least 4 points improvement in the severity of Peak Pruritus Numerical Rating Scale (PP-NRS).

Patients who received dupilumab and subsequently enrolled in EXTEND were randomized to either FREORLA 100 mg or 200 mg once daily upon entering EXTEND. Among responders to dupilumab in COMPARE, the majority maintained response 12 weeks after switching to FREORLA [77% and 86% for IGA (0 or 1) response, and 90% and 96% for EASI-75 with 100 mg once daily or 200 mg once daily, respectively]. Among non-responders to dupilumab in COMPARE, a substantial proportion of patients achieved response 12 weeks after switching to FREORLA [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].

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

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

Among patients who did not achieve IGA (0 or 1) response after 12 weeks of FREORLA treatment and entered EXTEND, 14% and 22% of patients continuing FREORLA 100 mg once daily in EXTEND achieved IGA (0 or 1) response by Week 16 and Week 24 (with 4 and 12 additional weeks of treatment), respectively, and 19% and 27% of patients continuing FREORLA 200 mg once daily achieved IGA response by Week 16 and Week 24, respectively. Among patients who did not achieve EASI-75 after 12 weeks of FREORLA treatment and entered EXTEND, 32% and 45% of patients continuing FREORLA 100 mg once daily in EXTEND achieved EASI-75 by Week 16 and Week 24 (with 4 and 12 additional weeks of treatment), respectively, and 34% and 54% of patients continuing FREORLA 200 mg once daily achieved EASI-75 response by Week 16 and Week 24, respectively.

*Long-term efficacy*
Among patients who achieved response at Week 12 of a qualifying parent study and entered EXTEND, the majority of patients maintained their response at Week 48 of cumulative FREORLA treatment for both doses of FREORLA [53% and 57% for IGA (0 or 1) response, 69% and 71% for EASI-75, and 52% and 69% for PP-NRS4 with 100 mg once daily and 200 mg once daily, respectively].

Health related outcomes

Treatment with either dose of FREORLA as monotherapy resulted in significantly improved patient-reported outcomes at 12 weeks compared with placebo (see Table 7). A significantly larger proportion of the FREORLA groups had clinically meaningful reductions in Dermatology Life Quality Index (DLQI) total scores (defined as a 4-point improvement) from baseline to Week 12 compared with placebo. FREORLA groups also had a significantly larger proportion of patients who reported “no effect” of their disease on their quality of life (as measured by a DLQI score of 0 or 1).

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

**Table 6. Additional endpoint results with FREORLA monotherapy at Week 12**

| | MONO-1 | | | MONO-2 | | |
|---|---|---|---|---|---|---|
| | ABR | | | ABR | | |
| | 200 mg QD N=154 | 100 mg QD N=156 | Placebo N=77 | 200 mg QD N=155 | 100 mg QD N=158 | Placebo N=78 |
| LSM SCORAD (sleep loss subscale) | | | | | | |
| Baseline median (SD) | 5.9 | 6.0 | 6.5 | 6.2 | 6.2 | 5.7 |
| Change from baseline (95% CI) | -3.7[d] (-4.2, -3.3) | -2.9[c] (-3.4, -2.5) | -1.6 (-2.2, -1.0) | -3.8[d] (-4.2, -3.4) | -3.0[a] (-3.4, -2.6) | -2.1 (-2.7, -1.5) |
| NTIS >4-point improvement | | | | | | |
| % responders | n/a | n/a | n/a | 57.0[d] | 42.7[d] | 12.7 |

**Table 6. Additional endpoint results with FREORLA monotherapy at Week 12**

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

Abbreviations: ABR=abrocitinib; CDLQI=Child Dermatology Life Quality Index; CI=confidence interval; DLQI=Dermatology Life Quality Index; HADS=Hospital Anxiety and Depression Scale; LSM=least squares mean; N=number of patients randomized; n/a= not available; NTIS=Night Time Itch Scale Severity; POEM=Patient Oriented Eczema Measure; QD=once daily; SCORAD=SCORing Atopic Dermatitis.

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

In COMPARE, a significantly larger proportion of the FREORLA groups had clinically meaningful reductions in DLQI total scores (defined as a 4-point improvement) from baseline to Week 12 compared with placebo (see Table 8). FREORLA groups also had a significantly larger proportion of patients who reported “no effect” of their disease on their quality of life (as measured by a DLQI score of 0 or 1).

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

**Table 7. Additional endpoint results with FREORLA in combination with medicated topical therapies at Week 12**

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

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

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

## 5.2. Pharmacokinetic properties

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

Absorption

*Effect of Food*
Abrocitinib is well-absorbed with over 91% extent of oral absorption and absolute oral bioavailability of approximately 60%. Both $C_{max}$ and AUC of abrocitinib increased dose proportionally up to 400 mg. Coadministration of FREORLA 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, FREORLA was administered without regard to food (see Section 4.2).

Distribution

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

Metabolism

The metabolism of abrocitinib is mediated by multiple CYP enzymes, CYP2C19 (~53%), CYP2C9 (~30%), CYP3A4 (~11%) and CYP2B6 (~6%). In a human radiolabeled study, abrocitinib was the most prevalent circulating species, with 3 polar mono-hydroxylated metabolites identified as M1 (3-hydroxypropyl), M2 (2-hydroxypropyl), and M4 (pyrrolidinone pyrimidine). 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 FREORLA 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.

Elimination

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

Special populations

*Body Weight, Gender, Genotype, Race, and Age*
Body weight, gender, CYP2C19/2C9 genotype, race, and age did not have a clinically meaningful effect on FREORLA exposure (see Section 4.2).

*Adolescents (12 to less than 18 years of age)*
Based on population pharmacokinetic analysis, mean FREORLA steady-state exposure in adolescent patients is estimated to be approximately 30% lower compared to adults of the same weight, with similar range of exposures in adult and adolescent patients. These differences in mean exposures were not considered clinically significant.

*Pediatric (under 12 years of age)*
The pharmacokinetics of FREORLA in pediatric patients under 12 years of age have not yet been established (see Section 4.2).

Renal impairment

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

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

**5.3 Preclinical safety data**

Genotoxicity

FREORLA is not mutagenic in the bacterial mutagenicity assay (Ames assay). Although FREORLA is aneugenic in the in vitro TK6 micronucleus assay, FREORLA is not aneugenic or clastogenic based on the results of the in vivo rat bone marrow micronucleus assay.

Carcinogenicity

No evidence of tumorigenicity was observed in Tg.rasH2 mice administered FREORLA for 26 weeks at oral doses up to 75 mg/kg/day and 60 mg/kg/day in female and male mice, respectively. In the 104-week oral carcinogenicity study, FREORLA resulted in statistically higher incidence of benign thymomas in female rats at exposures greater than or equal to 2.8 times the unbound human AUC at the MRHD of 200 mg. No evidence of FREORLA-related tumorigenicity was observed following oral FREORLA administration in female rats at exposures equal to 0.6 times the unbound human AUC at the MRHD of 200 mg or in male rats at exposures equal to 14 times the unbound human AUC at the MRHD of 200 mg.

Reproductive and developmental toxicity

FREORLA had no effects on male fertility or spermatogenesis at doses up to 70 mg/kg/day at exposures equal to 26 times the unbound human AUC at the MRHD of 200 mg. FREORLA

resulted in effects on female fertility (lower fertility index, corpora lutea, and implantation sites) at exposures equal to 29 times the unbound human AUC at the MRHD of 200 mg and higher postimplantation loss in rats at exposures greater than or equal to 11 times the unbound human AUC at the MRHD of 200 mg. The effects on female fertility in rats reversed 1 month after cessation of FREORLA administration. No effects on female fertility were noted at exposures equal to 2 times the unbound human AUC at the MRHD of 200 mg.

No fetal malformations were observed in embryo-fetal development studies in rats or rabbits. In an embryo-fetal development study in pregnant rabbits, oral administration of FREORLA during gestation days 7 to 19 had no effects on embryo-fetal survival or fetal morphological development at exposures equal to 4 times the unbound human AUC at the MRHD of 200 mg. FREORLA resulted in an increase incidence of delayed ossification of the forelimb phalanges at exposures equal to 4 times the unbound human AUC at the MRHD of 200 mg.

In an embryo-fetal development study in pregnant rats, oral administration of FREORLA during gestation days 6 to 17 resulted in increased embryo-fetal lethality at exposures equal to 17 times the unbound human AUC at the MRHD of 200 mg. No embryo-fetal lethality was observed in pregnant rats orally dosed with FREORLA during organogenesis at exposures equal to 11 times the unbound human AUC at the MRHD of 200 mg. FREORLA resulted in increased incidences of skeletal variations of short 13th ribs at exposures greater than or equal to 11 times the unbound human AUC at the MRHD of 200 mg and reduced ventral processes, thickened ribs, and unossified metatarsals at exposures equal to 17 times the unbound human AUC at the MRHD of 200 mg. No skeletal variations were noted in rats at exposures equal to 2.4 times the unbound human AUC at the MRHD of 200 mg.

In a rat pre- and postnatal development study in pregnant rats, oral administration of FREORLA during gestation day 6 through lactation day 21 resulted in dystocia with prolonged parturition and lower offspring body weights at exposures greater than or equal to 11 times the unbound human AUC at the MRHD of 200 mg and lower postnatal survival at exposures equal to 17 times the unbound human AUC at the MRHD of 200 mg. No maternal or developmental toxicity was observed in either dams or offspring at exposures equal to 2.4 times the unbound human AUC at the MRHD of 200 mg.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

Tablet core

Microcrystalline cellulose
Dibasic calcium phosphate anhydrous
Sodium starch glycolate
Magnesium stearate

Film-coat

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

**6.2. Incompatibilities**

Not applicable.

**6.3. Shelf life**

30 months.

**6.4. Special precautions for storage**

Store below 30ºC. Keep in original package.

**6.5. Nature and contents of container**

FREORLA 50 mg film-coated tablets

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

FREORLA 100 mg film-coated tablets

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

FREORLA 200 mg film-coated tablets

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

Not all pack sizes may be marketed.

**6.6. Special precautions for disposal and other handling**

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

## 7. MARKETING AUTHORISATION HOLDER

**Manufactured by:**
Pfizer Manufacturing Deutschland GmbH
Freiburg
Germany

**Imported by:**
PT. Pfizer Indonesia
Jakarta, Indonesia

## 8. MARKETING AUTHORISATION NUMBER(S)

FREORLA® 50 mg film-coated tablets, Box, 2 blister @ 7 film coated tablets; Reg. No.: DKXXXXXXXXXXX.
FREORLA® 100 mg film-coated tablets, Box, 2 blister @ 7 film coated tablets; Reg. No.: DKXXXXXXXXXXX.
FREORLA® 200 mg film-coated tablets, Box, 2 blister @ 7 film coated tablets; Reg. No.: DKXXXXXXXXXXX.

**HARUS DENGAN RESEP DOKTER**

## 9. DATE OF REVISION OF THE TEXT
12/2022

**PT. PFIZER INDONESIA**
**Local Product Document**

Generic Name: Abrocitinib
Trade Name: FREORLA
CDS Effective Date: June 04, 2021
Supersedes: NA

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FREORLA 50 mg film-coated tablets

Each film-coated tablet contains 50 mg abrocitinib

FREORLA 100 mg film-coated tablets

Each film-coated tablet contains 100 mg abrocitinib

FREORLA 200 mg film-coated tablets

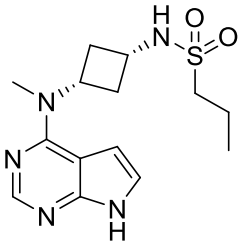
Each film-coated tablet contains 200 mg abrocitinib

Excipients with known effects

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

For a full list of excipients, see Section 6.1

Structure of abrocitinib:



## 3. PHARMACEUTICAL FORM

Film-coated tablet.

FREORLA 50 mg film-coated tablets
Pink, oval tablet 10.50 mm long and 4.75 mm wide, debossed with "PFE" on one side and "ABR 50" on the other.

FREORLA 100 mg film-coated tablets
Pink, round tablet 9.00 mm in diameter, debossed with "PFE" on one side and "ABR 100" on the other.

FREORLA 200 mg film-coated tablets
Pink, oval tablet 18.42 mm long and 8.00 mm wide debossed with "PFE" on one side and "ABR 200" on the other.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

FREORLA is indicated for the treatment of adult patients with age 18 years or older with moderate-to-severe atopic dermatitis, including the relief of pruritus, who have had an inadequate response to prescribed topical therapy or for whom these treatments are not advisable. FREORLA can be used with or without medicated topical therapies for atopic dermatitis.

### 4.2. Posology and method of administration

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

Posology

The recommended dose of FREORLA is 100 mg or 200 mg once daily, based on individual goal of therapy and potential risk for adverse reactions.

- A starting dose of 100 mg once daily is recommended for patients more than equal to 65 years of age. For other patients who may benefit from a starting dose of 100 mg (see Sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects).

- During treatment, the dose may be decreased or increased based on tolerability and efficacy. The lowest effective dose for maintenance should be considered. The maximum daily dose is 200 mg.

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

FREORLA should be taken orally once daily with or without food at approximately the same time each day.

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

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

*Laboratory monitoring*

**Table 1. Laboratory Measures and Monitoring Guidance**

| Laboratory measure | 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 hyperlipidemia. |

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

*Dose interruption*
If a patient develops a serious infection, sepsis or opportunistic infection, consider interruption of FREORLA until the infection is controlled should be considered (see Section 4.4).

Interruption of dosing may be needed for management of laboratory abnormalities as described in Table 2 (see Section 4.4).

*Drug-drug 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. Treatment is not recommended concomitantly with moderate or strong inducers of CYP2C19/CYP2C9 enzymes (e.g. rifampicin, apalutamide, efavirenz, enzalutamide, phenytoin).
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 less than 60 mL/min) renal impairment, the recommended dose of abrocitinib should be reduced by half to 100 mg or 50 mg once daily. In patients with severe (eGFR less than 30 mL/min) renal impairment, 50 mg once daily is the recommended starting dose. The maximum daily dose is 100 mg. The use of FREORLA 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. FREORLA has not been studied in patients with severe (Child Pugh C) hepatic impairment (see Section 5.2).

*Elderly population*
The recommended starting dose for patients aged 65 years or more is 100 mg once daily.
*Pediatric population*
FREORLA is not recommended for pediatric patients under 18 years of age. The safety and efficacy of FREORLA in pediatric patients under 12 years of age have not yet been established. No data are available.

Method of administration

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

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

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

**4.3. Contraindications**

- Hypersensitivity to the active substance or to any of the excipients listed.

- Active serious systemic infections, including tuberculosis (TB).
- Severe hepatic impairment.
- Pregnancy and breast-feeding.

**4.4. Special warnings and precautions for use**

Serious infections

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

Treatment must not be initiated in patients with an active, serious systemic infections.

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 FREORLA. A patient who develops a new infection during treatment with FREORLA should undergo prompt and complete diagnostic testing and appropriate antimicrobial therapy should be initiated. The patient should be closely monitored and FREORLA therapy should be interrupted if the patient is not responding to standard therapy.

*Tuberculosis*
Patients should be screened for tuberculosis (TB) before starting FREORLA therapy and consider yearly screening for patients in highly endemic areas for TB. FREORLA should not be given to patients with active TB. 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 FREORLA.

*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 65 years of age and older and patients with severe atopic dermatitis at baseline. 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 with FREORLA. Patients with evidence of active hepatitis B or hepatitis C (positive hepatitis C PCR) infection were excluded from clinical studies (see Section 5.2). Patients who were hepatitis B surface antigen negative, hepatitis B core antibody positive, and hepatitis B surface antibody positive had testing for hepatitis B virus (HBV) DNA.

Patients who had HBV DNA above the lower limit of quantification (LLQ) were excluded. Patients who had HBV DNA negative or below LLQ could initiate treatment with FREORLA; 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. Avoid use of live, attenuated vaccines during or immediately prior to FREORLA therapy is not recommended. Prior to initiating FREORLA, it is recommended that patients be brought up to date with all immunizations, including prophylactic herpes zoster vaccinations, in agreement with current immunization guidelines.

Venous thromboembolism

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving Janus kinase (JAK) inhibitors including FREORLA (see Section 4.8). FREORLA should be used with caution in patients at high risk for DVT/PE. Risk factors that should be considered in determining the patient's risk for DVT/PE include older age, obesity, a medical history of DVT/PE, prothrombotic disorder, use of combined hormonal contraceptives or hormone replacement therapy, patients undergoing major surgery, or prolonged immobilization. If clinical features of DVT/PE occur, FREORLA treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.

Malignancy (including non-melanoma skin cancers)

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

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

Hematologic 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 FREORLA should not be initiated in patients with a platelet count $<150 \times 10^3/mm^3$, an ALC $<0.5 \times 10^3/mm^3$, an ANC $<1 \times 10^3/mm^3$ or who have a hemoglobin value <8 g/dL (see Section 4.2). Platelet count and ALC should be monitored 4 weeks after initiation of therapy with FREORLA and thereafter according to routine patient management.

Lipids

Dose-dependent increase in blood lipid parameters were reported in patients treated with FREORLA (see Section 4.8). Lipid parameters should be assessed approximately 4 weeks following initiation of FREORLA therapy and thereafter patients should be managed according to clinical guidelines for hyperlipidemia. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined. Patients with abnormal lipid parameters should be further monitored and managed according to clinical guidelines, due to the known cardiovascular risks associated with hyperlipidaemia. In patients with a high burden of cardiovascular risk factors, the risks and benefits of abrocitinib compared to that of other available therapies for atopic dermatitis should be considered. If abrocitinib is chosen, interventions to manage lipid concentrations should be implemented according to clinical guidelines.

**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.

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

**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 FREORLA

Abrocitinib is metabolized 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.

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

*Coadministration with CYP2C19/CYP2C9 inducers*
Administration of FREORLA 200 mg after multiple dosing with rifampin, a strong inducer of CYP enzymes, resulted in reduction of abrocitinib active moiety exposures by approximately 56%.

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

*Co-administration with products which increase gastric pH*
The effect of elevating gastric pH with antacids, H2-receptor antagonists (famotidine), or proton pump inhibitors (omeprazole) on the pharmacokinetics of abrocitinib has not been studied and may reduce the absorption of abrocitinib due to the low solubility of abrocitinib at pH above 4.

Potential for FREORLA to affect pharmacokinetics of other medicines

In vitro, abrocitinib or its metabolites were not significant inhibitors or inducers of CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) or of uridine diphosphate-glucuronyltransferases (UGTs) (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7). In vitro, abrocitinib is an inhibitor of P-glycoprotein (P-gp), organic anion transporter (OAT)3, organic cation transporter (OCT)1, multidrug and toxin compound extrusion protein (MATE)1/2K and breast cancer resistance protein (BCRP) but is not an inhibitor of organic anion transporting polypeptide (OATP)1B1/1B3, bile salt export pump (BSEP), OAT1 or OCT2 at clinically meaningful concentrations. The metabolites do not change the transporter inhibition risk compared to abrocitinib.
No clinically significant effects of FREORLA were observed in drug interaction studies with oral contraceptives (e.g., ethinyl estradiol/levonorgestrel), or with substrates of BCRP and OAT3 (e.g., rosuvastatin), MATE1/2K (e.g., metformin) and CYP3A4 (e.g., midazolam).
Coadministration of dabigatran etexilate (a P-gp substrate), with a single dose of FREORLA 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 inducer of CYP2B6 and CYP1A2, and an inducer and inhibitor of CYP2C19 enzymes. Pharmacokinetic interaction studies have not been performed with subtrates of CYP2B6, CYP1A2 and CYP2C19. The exposures of medicinal products metabolized by CYP2B6 (e.g., bupropion, efavirenz) and CYP1A2 (e.g., alosetron, duloxetine, ramelteon, tizanidine) may be decreased and of those metabolized by CYP2C19 (e.g., S-mephenytoin) may be increased initially and then decreased, when used concomitantly with abrocitinib.

## 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 FREORLA. Consider pregnancy planning and prevention for females of reproductive potential.

Pregnancy

The limited human data on use of FREORLA in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage. In embryo-fetal development studies, oral administration of FREORLA to pregnant rats during organogenesis resulted in fetotoxicity at exposures equal to 17 times the unbound AUC at the maximum recommended human dose (MRHD) of 200 mg once daily. In embryo-fetal development studies, oral administration of FREORLA to pregnant rabbits did not result in fetotoxicity at exposures equal to 4 times the unbound AUC at the MRHD of 200 mg. In a pre- and postnatal development study in pregnant rats, FREORLA oral administration during gestation and through lactation resulted in lower postnatal survival and lower offspring body weights at exposures greater than or equal to 11 times the unbound AUC at the MRHD of 200 mg once daily (see Section 5.3). FREORLA is contraindicated during pregnancy.

Breastfeeding

There are no data on the presence of FREORLA in human milk, the effects on the breastfed infant, or the effects on milk production. FREORLA was secreted in milk of lactating rats. A risk to newborns/infants cannot be excluded and FREORLA is contraindicated during breast-feeding.

Fertility

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

## 4.7. Effects on ability to drive and use machines

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

## 4.8. Undesirable effects

Summary of safety profile

The most commonly reported adverse reactions (ARs) occurring in ⩾2% of patients treated with FREORLA in placebo-controlled studies were nausea (10.3%), headache (6.8%), herpes simplex (3.8%), acne (3.2%), blood creatine phosphokinase increased (2.6%), dizziness (2.3%), and

vomiting (2.3%). The most frequent serious adverse reactions in atopic dermatitis patients were infections (see Section 4.4).

Tabulated list of adverse reactions

A total of 2856 patients were treated with FREORLA in clinical studies in atopic dermatitis representing 1614 patient-years of exposure. There were 606 patients with more than 1 year of exposure to FREORLA. Four placebo-controlled studies were integrated (608 patients on 100 mg once daily, 590 patients on 200 mg once daily and 342 patients on placebo) to evaluate the safety of FREORLA in comparison to placebo for up to 16 weeks.

**Table 2. Adverse reactions for FREORLA**

| **System Organ Class** | **Very Common ≥1/10** | **Common ≥1/100 to <1/10** | **Uncommon ⩾1/1,000 to <1/100** |
|---|---|---|---|
| Infections and infestations | | Herpes simplex[a] | Herpes zoster[b]<br>Pneumonia |
| Blood and lymphatic system disorders | | | Thrombocytopenia<br>Lymphopenia |
| Metabolism and nutrition disorders | | | Hyperlipidaemia[c] |
| Nervous system disorders | | Headache<br>Dizziness | |
| Vascular disorders | | | Venous thromboembolism[d] |
| Gastrointestinal disorders | Nausea | Vomiting<br>Abdominal pain upper | |
| Skin and subcutaneous tissue disorders | | Acne | |
| Investigations | | Blood creatine phosphokinase increased | |

a. Herpes simplex includes oral herpes, ophthalmic herpes simplex, genital herpes, and herpes dermatitis.
b. Herpes zoster includes ophthalmic herpes zoster.
c. Hyperlipidaemia included dyslipidaemia and hypercholesterolaemia.
d. Venous thromboembolism includes pulmonary embolism and deep vein thrombosis.

Description of selected adverse reactions

*Overall infections*
In placebo-controlled studies, for up to 16 weeks, overall infections have been reported in 26.3% of patients treated with placebo and in 35.2% and 34.6% of patients treated with FREORLA 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 (0.61 per 100 patient-years in the abrocitinib 100 mg group and 1.23 per 100 patient-years in the abrocitinib 200 mg group ), most of which were non-serious multidermatomal cutaneous infections. Among all patients treated in clinical studies with consistent dosing regimens of either abrocitinib 100 mg or 200 mg, including the long-term extension study, the incidence rate of herpes zoster in patients treated with abrocitinib 200 mg (4.83 per 100 patient-years) was higher than that of patients treated with 100 mg (2.39 per 100 patient-years). Incidence rates for herpes zoster were also higher for patients 65 years of age and older (HR 3.68), patients with a medical history of herpes zoster (HR 3.61), patients with severe atopic dermatitis at baseline (HR 1.28), and a confirmed ALC < $1.0 \times 10^3$ /$mm^3$ prior to the event of herpes zoster (HR 1.84).

*Serious infections*
In placebo-controlled studies, for up to 16 weeks, serious infections have been reported in 2 patients (2.31 per 100 patient-years) treated with placebo, 6 patients (3.80 per 100 patient-years) treated with FREORLA 100 mg, and 2 patients (1.28 per 100 patient-years) treated with FREORLA 200 mg. Among all patients treated with FREORLA, including the long-term extension study, serious infections were reported in 17 patients (2.65 per 100 patient-years) treated with FREORLA 100 mg and 24 patients (2.33 per 100 patient-years) treated with FREORLA 200 mg. The most commonly reported serious infections were herpes simplex, herpes zoster, and pneumonia (see Section 4.4).

*Opportunistic infections*
All observed opportunistic infections were cases of multidermatomal cutaneous herpes zoster. Among all patients treated with FREORLA, including the long-term extension study, opportunistic infections were reported in 3 patients (0.47 per 100 patient-years) treated with FREORLA 100 mg and 10 patients (0.97 per 100 patient-years) treated with FREORLA 200 mg. Most cases of opportunistic herpes zoster were mild or moderate.

*Venous thromboembolism*
Among all patients treated with FREORLA, including the long-term extension study, PE was reported in 3 patients (0.18 per 100 patient-years), all treated with FREORLA 200 mg. Events of

DVT were reported in 2 patients (0.09 per 100 patient-years) treated with FREORLA 200 mg (see Section 4.4).

*Thrombocytopenia*
In placebo-controlled studies, for up to 16 weeks, treatment with FREORLA 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 1 patient (0.1%) exposed to FREORLA 200 mg, 0 patients treated with FREORLA 100 mg or placebo. Among all patients exposed to FREORLA, including the long-term extension study, confirmed platelet counts of $<50 \times 10^3/mm^3$ were reported in 2 patients (0.1%), both treated with FREORLA 200 mg (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 2 patients (0.3%) treated with FREORLA 200 mg and 0 patients treated with FREORLA 100 mg or placebo. Both cases occurred in the first 4 weeks of exposure. Among all patients exposed to FREORLA, including the long-term extension, confirmed ALC $<0.5 \times 10^3/mm^3$ were reported in 4 patients (0.1%) treated with 200 mg of FREORLA and 0 patients treated with FREORLA 100 mg (see Section 4.4).

*Lipid elevations*
In placebo-controlled studies, for up to 16 weeks, there was a dose-related percent increase in low-density lipoprotein cholesterol (LDL-c), total cholesterol, and high-density lipoprotein cholesterol (HDL-c) relative to placebo at Week 4 which remained elevated through the final visit in the treatment period. There was no change in the LDL/HDL ratio or triglycerides. Events related to hyperlipidemia occurred in 1 patient (0.2%) exposed to FREORLA 100 mg, 7 patients (1.2%) exposed to FREORLA 200 mg and 0 patients exposed to placebo (see Section 4.4).

*Creatine phosphokinase elevations (CPK)*
In placebo-controlled studies, for up to 16 weeks, events of blood CPK increased were reported in 1.5% of patients treated with placebo, 2.3% and 2.9% of patients treated with 100 mg and 200 mg of FREORLA, respectively.[43] Most elevations were transient, and none led to discontinuation. In the clinical studies, there were no reported events of rhabdomyolysis.

*Nausea*
Nausea was most frequent in the first week of FREORLA therapy and generally resolved with continued therapy. The median duration of nausea was 15 days. Most of the cases were mild to moderate in severity.
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.

Pediatric population

The pharmacokinetics, safety and efficacy of FREORLA in pediatric patients under 12 years of age have not yet been established.

Of the 2856 patients with atopic dermatitis exposed to FREORLA, a total of 364 adolescents (12 to less than 18 years of age) were enrolled in FREORLA studies. The safety profile observed in adolescents in atopic dermatitis clinical studies was similar to that of the adult population. There were no adolescent patients who developed platelet counts $<75 \times 10^3/mm^3$ or absolute lymphocyte count $<0.5 \times 10^3/mm^3$.

Elderly population

A total of 145 patients 65 years of age and older were enrolled in FREORLA studies. The safety profile observed in elderly patients was similar to that of the adult population overall. A higher proportion of patients 65 years of age and older discontinued from clinical studies compared to younger patients. Among all patients exposed to FREORLA including the long-term extension study, confirmed ALC $<0.5 \times 10^3/mm^3$ occurred only in patients 65 years of age and older. A higher proportion of patients 65 years of age and older had platelet counts $<75 \times 10^3/mm^3$. The incidence rate of herpes zoster in patients 65 years of age and older treated with FREORLA (7.40 per 100 patient-years) was higher than that of patients 18 to less than 65 years of age (3.44 per 100 patient-years) and less than 18 years of age (2.12 per 100 patient-years). There is limited data in patients above 75 years of age.

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.

**4.9. Overdose**

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

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

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1. Pharmacodynamic properties

Mechanism of action

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

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

Pharmacodynamic effects

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

Clinical efficacy and safety

The efficacy and safety of FREORLA as monotherapy and in combination with background medicated topical therapies were evaluated in 3 pivotal randomized, double-blind, placebo-controlled studies (MONO-1, MONO-2, and COMPARE) in 1616 patients 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, body surface area (BSA) involvement ≥10%, and Peak Pruritus Numerical Rating Scale (PP-NRS) ≥4 at the baseline visit prior to randomization.

Patients in these studies were those who had inadequate response to previous topical medication, or were patients for whom topical treatments were medically inadvisable, or who had received systemic therapies including dupilumab. In each of the pivotal studies, over 40% of patients had

prior exposure to systemic therapy. In MONO-1 and MONO-2, 6% of the patients had received dupilumab, whereas prior use of dupilumab was not allowed in COMPARE.

Eligible patients from qualifying parent studies were able to enroll in the long-term extension study EXTEND, e.g., if they completed the full treatment period of the any of the pivotal qualifying parent studies.

MONO-1, MONO-2, and COMPARE assessed the co-primary endpoints of IGA and EASI-75 responses at Week 12. Key secondary endpoints in MONO-1 and MONO-2 included improvement of ≥4 points in the severity of PP-NRS (PP-NRS4) at Week 12 and change from baseline to Week 12 for the Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD). The PSAAD is an 11-item, self-reported instrument using a 24-hour recall period, designed to assess the severity of key symptoms and signs of atopic dermatitis including itching, pain, dryness, flaking, cracking, bumps, redness, discoloration, bleeding, fluid, and swelling. Key secondary endpoints in COMPARE were PP-NRS4 at Week 2 in addition to IGA response and EASI-75 at Week 16. The designs of the pivotal and long-term extension studies are summarized in Table 4.

**Table 3. Clinical study summary**

| **Study name (regimen type)**<br><br>**Treatment duration** | **Population (number of randomized patients)** | **Treatment arms** | **Primary and key secondary endpoints** |
|---|---|---|---|
| MONO-1 (monotherapy)<br><br>12 weeks | Adults and adolescents (387) | • FREORLA 200 mg QD<br>• FREORLA 100 mg QD<br>• Placebo | Co-primary<br>• IGA response[a] at Week 12<br>• EASI-75[b] at Week 12<br><br>Key secondary<br>• PP-NRS4[c] at Weeks 2, 4 and 12<br>• Change from baseline in PSAAD[d] at Week 12 |
| MONO-2 (monotherapy)<br><br>12 weeks | Adults and adolescents (391) | • FREORLA 200 mg QD<br>• FREORLA 100 mg QD<br>• Placebo | Co-primary<br>• IGA response at Week 12<br>• EASI-75 at Week 12<br><br>Key secondary<br>• PP-NRS4 at Weeks 2, 4 and 12<br>• Change from baseline in PSAAD at Week 12 |
| COMPARE (combination therapy) | Adults (838) | • FREORLA 200 mg QD<br>• FREORLA 100 mg QD<br>• Placebo | Co-primary<br>• IGA response at Week 12<br>• EASI-75 at Week 12 |

| | | | |
|---|---|---|---|
| 16 weeks | | • Dupilumab 300 mg Q2W SC[e]<br><br>All patients received background medicated topical therapy | Key secondary<br>• PP-NRS4 at Week 2<br>• IGA response at Week 16<br>• EASI-75 at Week 16 |
| EXTEND (long-term extension)<br><br>variable | Adults and adolescents (approximately 2300) | • FREORLA 200 mg QD<br>• FREORLA 100 mg QD | Primary<br>• Long-term safety |

Primary and key secondary endpoints were controlled for multiplicity.
Abbreviations: EASI=Eczema Area and Severity Index; IGA=Investigator Global Assessment; PP-NRS=Peak Pruritus Numerical Rating Scale; PSAAD=Pruritus and Symptoms Assessment for Atopic Dermatitis; QD=once daily; Q2W=once every 2 weeks; SC=subcutaneously.

a. IGA response was based on 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 was based on ⩾75% improvement in EASI from baseline.
c. PP-NRS4 response was based on an improvement of ⩾4 points in the severity of PP-NRS.
d. PSAAD ranges from 0 to 10 with higher scores indicating greater levels of atopic dermatitis symptom severity.
e. Dupilumab treatment in COMPARE: An initial dose of 600 mg on day 1, followed by 300 mg Q2W.

*Clinical response*

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

*Monotherapy studies*

In both pivotal monotherapy studies (MONO-1, MONO-2), the proportion of patients who achieved IGA and/or EASI-75 response was significantly higher in patients who received FREORLA 100 mg or 200 mg once daily compared with placebo at Week 12 (see Table 5).

A significantly higher proportion of patients who achieved PP-NRS4 (defined as an improvement of ≥4 points in the severity of PP-NRS) with FREORLA 100 mg or 200 mg once daily compared with placebo was observed as soon as Week 2 and persisting through Week 12. Higher proportions of patients achieved PP-NRS4 with FREORLA 100 mg or 200 mg once daily compared with placebo by Day 6 and Day 3 (2 days after the first dose), respectively (see Table 5).

**Table 4. Efficacy results of FREORLA monotherapy at Week 12**

| | **MONO-1** | | | **MONO-2** | | |
|---|---|---|---|---|---|---|
| | **ABR** | | | **ABR** | | |
| | **200 mg QD N=154** | **100 mg QD N=156** | **Placebo N=77** | **200 mg QD N=155** | **100 mg QD N=158** | **Placebo N=78** |
| | **% Responders (95% CI)** | | | | | |
| IGA 0 or 1[a] | 43.8[g] (35.9, 51.7) | 23.7[e] (17.0, 30.4) | 7.9 (1.8, 14.0) | 38.1[g] (30.4, 45.7) | 28.4[f] (21.3, 35.5) | 9.1 (2.7, 15.5) |
| EASI-50[b] | 75.8[k] (69.0, 82.6) | 57.7[k] (49.9, 65.4) | 22.4 (13.0, 31.7) | 79.9[k] (73.5, 86.2) | 68.4[k] (61.1, 75.7) | 19.5 (10.6, 28.3) |
| EASI-75[b] | 62.7[g] | 39.7[g] | 11.8 | 61.0[g] | 44.5[g] | 10.4 |

**Table 4. Efficacy results of FREORLA monotherapy at Week 12**

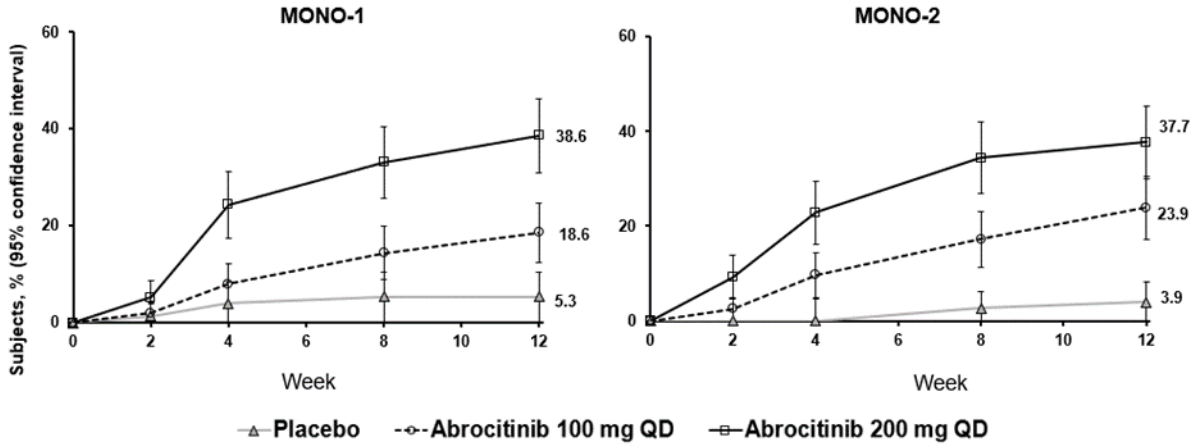
| | MONO-1 | | | MONO-2 | | |
|---|---|---|---|---|---|---|
| | ABR | | | ABR | | |
| | 200 mg QD N=154 | 100 mg QD N=156 | Placebo N=77 | 200 mg QD N=155 | 100 mg QD N=158 | Placebo N=78 |
| | (55.1, 70.4) | (32.1, 47.4) | (4.6, 19.1) | (53.3, 68.7) | (36.7, 52.3) | (3.6, 17.2) |
| EASI-90[b] | 38.6[k] (30.8, 46.3) | 18.6[i] (12.5, 24.7) | 5.3 (0.2, 10.3) | 37.7[k] (30.0, 45.3) | 23.9[k] (17.2, 30.6) | 3.9 (0.0, 8.2) |
| EASI-100[b] | 13.1[i] (7.7, 18.4) | 6.4[h] (2.6, 10.3) | 0 (0.0, 4.7) | 7.1[h] (3.1, 11.2) | 5.2[h] (1.7, 8.6) | 0 (0.0, 4.7) |
| PP-NRS4[c,d] | 57.2[g] (48.8, 65.6) | 37.7[f] (29.2, 46.3) | 15.3 (6.6, 24.0) | 55.3[g] (47.2, 63.5) | 45.2[g] (37.1, 53.3) | 11.5 (4.1, 19.0) |
| PP-NRS (0 or 1) | 35.4[k] (27.2, 43.6) | 21.1[i] (13.9, 28.4) | 3.2 (0.0, 7.5) | 32.4[k] (24.5, 40.2) | 21.3[i] (14.5, 28.0) | 5.5 (0.3, 10.7) |
| | % Change from baseline (95% CI) | | | | | |
| LSM EASI | -73.5[k] (-79.1, -68.0) | -57.5[k] (-63.1, -51.9) | -28.4 (-36.5, -20.3) | -73.3[k] (-79.7, -66.9) | -60.0[k] (-66.5, -53.6) | -28.6 (-38.4, -18.8) |
| LSM PP-NRS | -56.5[k] (-63.6, -49.5) | -39.5[i] (-46.7, -32.3) | -19.5 (-30.0, -9.0) | -56.9[k] (-64.0, -49.8) | -43.5[j] (-50.7, -36.3) | -20.8 (-31.6, -9.9) |
| LSM SCORAD | -55.1[k] (-60.1, -50.2) | -41.5[k] (-46.5, -36.5) | -21.6 (-28.7, -14.5) | -56.2[k] (-61.2, -51.1) | -45.8[k] (-50.9, -40.7) | -22.7 (-30.4, -15.1) |
| | Change from baseline (95% CI) | | | | | |
| LSM PSAAD | -3.2[g] (-3.6, -2.8) | -2.2[e] (-2.6, -1.9) | -1.1 (-1.7, -0.6) | -3.0[g] (-3.3, -2.7) | -2.4[g] (-2.8, -2.1) | -0.8 (-1.3, -0.3) |

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

a. IGA responders were patients with IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥ 2 points.
b. EASI-50, -75, -90 and -100 responders were patients with ≥50%, ≥75%, ≥90%, and ≥100% improvement, respectively in EASI, from baseline.
c. The proportion of PP-NRS4 responders was also significantly higher with FREORLA 200 mg and 100 mg once daily than placebo at Week 2, Week 4, and Week 8 in both MONO-1 and MONO-2.
d. PP-NRS4 responders were patients with ≥4-point improvement in PP-NRS from baseline.
e. Multiplicity-controlled p <0.01 versus placebo.
f. Multiplicity-controlled p <0.001 versus placebo.
g. Multiplicity-controlled p <0.0001 versus placebo.
h. Nominal p <0.05 versus placebo.
i. Nominal p <0.01 versus placebo.
j. Nominal p <0.001 versus placebo.
k. Nominal p <0.0001 versus placebo.

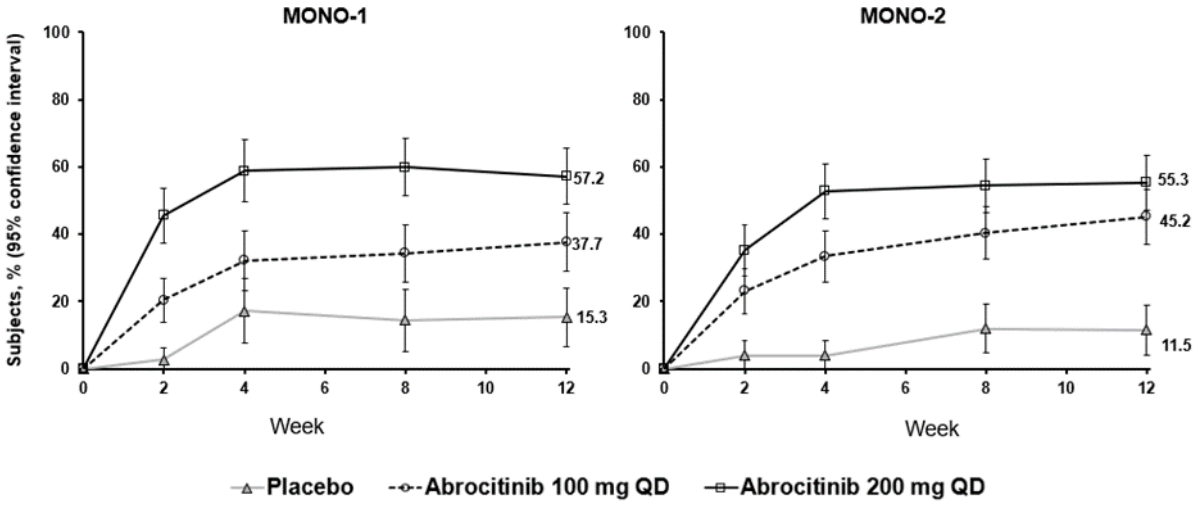
The proportion of patients who achieved EASI-90 or PP-NRS4 over time in studies MONO-1 and MONO-2 are shown in Figures 1 and 2.

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




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

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




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

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

*Combination therapy study*

In the pivotal combination therapy study (COMPARE), the proportion of patients who achieved IGA or EASI-75 response was significantly higher in patients who received FREORLA 100 mg or 200 mg once daily compared with placebo at Week 12 (see Table 6).

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

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

**Table 5. Efficacy results of FREORLA with concomitant topical therapy**

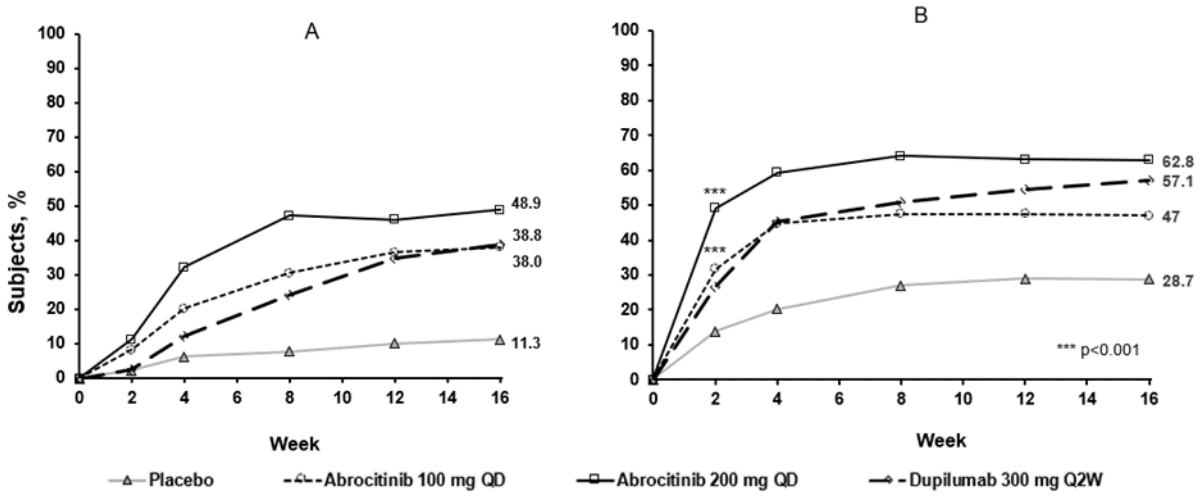
| | Week 2 | | | | Week 12 | | | | Week 16 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ABR | | | | ABR | | | | ABR | | | |
| | 200 mg N=226 | 100 mg N=238 | PBO N=131 | DUP N=243 | 200 mg N=226 | 100 mg N=238 | PBO N=131 | DUP N=243 | 200 mg N=226 | 100 mg N=238 | PBO N=131 | DUP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

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

a. IGA responders were patients with IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥ 2 points.
b. EASI-50, -75, -90 and -100 responders were patients with ≥50%, ≥75%, ≥90% and ≥100% improvement in EASI, respectively, from baseline.
c. PP-NRS4 responders were patients with ≥4-point improvement in PP-NRS from baseline.
d. Multiplicity-controlled p <0.001 vs. placebo
e. Multiplicity-controlled p <0.0001 vs. placebo
f. Multiplicity-controlled p <0.0001 vs. dupilumab. Statistical comparison between either abrocitinib dose and dupilumab was only performed on the proportion of patients achieving PP-NRS4 at Week 2.
g. Nominal p <0.05 vs. placebo
h. Nominal p <0.01 vs. placebo
i. Nominal p <0.001 vs. placebo
j. Nominal p <0.0001 vs. placebo

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

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




Abbreviations: EASI=Eczema Area and Severity Index; PP-NRS=Peak Pruritus Numerical Rating Scale; QD=once daily; Q2W=every 2 weeks.
EASI-90 was based on EASI ≥90% improvement from baseline.
PP-NRS4 response was based on achieving at least 4 points improvement in the severity of Peak Pruritus Numerical Rating Scale (PP-NRS).

Patients who received dupilumab and subsequently enrolled in EXTEND were randomized to either FREORLA 100 mg or 200 mg once daily upon entering EXTEND. Among responders to dupilumab in COMPARE, the majority maintained response 12 weeks after switching to FREORLA [77% and 86% for IGA (0 or 1) response, and 90% and 96% for EASI-75 with 100 mg once daily or 200 mg once daily, respectively]. Among non-responders to dupilumab in COMPARE, a substantial proportion of patients achieved response 12 weeks after switching to FREORLA [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].

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

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

Among patients who did not achieve IGA (0 or 1) response after 12 weeks of FREORLA treatment and entered EXTEND, 14% and 22% of patients continuing FREORLA 100 mg once daily in EXTEND achieved IGA (0 or 1) response by Week 16 and Week 24 (with 4 and 12 additional weeks of treatment), respectively, and 19% and 27% of patients continuing FREORLA 200 mg once daily achieved IGA response by Week 16 and Week 24, respectively. Among patients who did not achieve EASI-75 after 12 weeks of FREORLA treatment and entered EXTEND, 32% and 45% of patients continuing FREORLA 100 mg once daily in EXTEND achieved EASI-75 by Week 16 and Week 24 (with 4 and 12 additional weeks of treatment), respectively, and 34% and 54% of patients continuing FREORLA 200 mg once daily achieved EASI-75 response by Week 16 and Week 24, respectively.

*Long-term efficacy*
Among patients who achieved response at Week 12 of a qualifying parent study and entered EXTEND, the majority of patients maintained their response at Week 48 of cumulative FREORLA treatment for both doses of FREORLA [53% and 57% for IGA (0 or 1) response, 69% and 71% for EASI-75, and 52% and 69% for PP-NRS4 with 100 mg once daily and 200 mg once daily, respectively].

Health related outcomes

Treatment with either dose of FREORLA as monotherapy resulted in significantly improved patient-reported outcomes at 12 weeks compared with placebo (see Table 7). A significantly larger proportion of the FREORLA groups had clinically meaningful reductions in Dermatology Life Quality Index (DLQI) total scores (defined as a 4-point improvement) from baseline to Week 12 compared with placebo. FREORLA groups also had a significantly larger proportion of patients who reported “no effect” of their disease on their quality of life (as measured by a DLQI score of 0 or 1).

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

**Table 6. Additional endpoint results with FREORLA monotherapy at Week 12**

| | MONO-1 | | | MONO-2 | | |
|---|---|---|---|---|---|---|
| | ABR | | | ABR | | |
| | 200 mg QD N=154 | 100 mg QD N=156 | Placebo N=77 | 200 mg QD N=155 | 100 mg QD N=158 | Placebo N=78 |
| LSM SCORAD (sleep loss subscale) | | | | | | |
| Baseline median (SD) | 5.9 | 6.0 | 6.5 | 6.2 | 6.2 | 5.7 |
| Change from baseline (95% CI) | -3.7[d] (-4.2, -3.3) | -2.9[c] (-3.4, -2.5) | -1.6 (-2.2, -1.0) | -3.8[d] (-4.2, -3.4) | -3.0[a] (-3.4, -2.6) | -2.1 (-2.7, -1.5) |
| NTIS >4-point improvement | | | | | | |
| % responders | n/a | n/a | n/a | 57.0[d] | 42.7[d] | 12.7 |

**Table 6. Additional endpoint results with FREORLA monotherapy at Week 12**

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

Abbreviations: ABR=abrocitinib; CDLQI=Child Dermatology Life Quality Index; CI=confidence interval; DLQI=Dermatology Life Quality Index; HADS=Hospital Anxiety and Depression Scale; LSM=least squares mean; N=number of patients randomized; n/a= not available; NTIS=Night Time Itch Scale Severity; POEM=Patient Oriented Eczema Measure; QD=once daily; SCORAD=SCORing Atopic Dermatitis.

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

In COMPARE, a significantly larger proportion of the FREORLA groups had clinically meaningful reductions in DLQI total scores (defined as a 4-point improvement) from baseline to Week 12 compared with placebo (see Table 8). FREORLA groups also had a significantly larger proportion of patients who reported “no effect” of their disease on their quality of life (as measured by a DLQI score of 0 or 1).

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

**Table 7. Additional endpoint results with FREORLA in combination with medicated topical therapies at Week 12**

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

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

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

## 5.2. Pharmacokinetic properties

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

Absorption

*Effect of Food*

Abrocitinib is well-absorbed with over 91% extent of oral absorption and absolute oral bioavailability of approximately 60%. Both $C_{max}$ and AUC of abrocitinib increased dose proportionally up to 400 mg. Coadministration of FREORLA 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, FREORLA was administered without regard to food (see Section 4.2).

Distribution

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

Metabolism

The metabolism of abrocitinib is mediated by multiple CYP enzymes, CYP2C19 (~53%), CYP2C9 (~30%), CYP3A4 (~11%) and CYP2B6 (~6%). In a human radiolabeled study, abrocitinib was the most prevalent circulating species, with 3 polar mono-hydroxylated metabolites identified as M1 (3-hydroxypropyl), M2 (2-hydroxypropyl), and M4 (pyrrolidinone pyrimidine). 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 FREORLA 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.

Elimination

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

Special populations

*Body Weight, Gender, Genotype, Race, and Age*
Body weight, gender, CYP2C19/2C9 genotype, race, and age did not have a clinically meaningful effect on FREORLA exposure (see Section 4.2).

*Adolescents (12 to less than 18 years of age)*
Based on population pharmacokinetic analysis, mean FREORLA steady-state exposure in adolescent patients is estimated to be approximately 30% lower compared to adults of the same weight, with similar range of exposures in adult and adolescent patients. These differences in mean exposures were not considered clinically significant.

*Pediatric (under 12 years of age)*
The pharmacokinetics of FREORLA in pediatric patients under 12 years of age have not yet been established (see Section 4.2).

Renal impairment

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

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

**5.3 Preclinical safety data**

Genotoxicity

FREORLA is not mutagenic in the bacterial mutagenicity assay (Ames assay). Although FREORLA is aneugenic in the in vitro TK6 micronucleus assay, FREORLA is not aneugenic or clastogenic based on the results of the in vivo rat bone marrow micronucleus assay.

Carcinogenicity

No evidence of tumorigenicity was observed in Tg.rasH2 mice administered FREORLA for 26 weeks at oral doses up to 75 mg/kg/day and 60 mg/kg/day in female and male mice, respectively. In the 104-week oral carcinogenicity study, FREORLA resulted in statistically higher incidence of benign thymomas in female rats at exposures greater than or equal to 2.8 times the unbound human AUC at the MRHD of 200 mg. No evidence of FREORLA-related tumorigenicity was observed following oral FREORLA administration in female rats at exposures equal to 0.6 times the unbound human AUC at the MRHD of 200 mg or in male rats at exposures equal to 14 times the unbound human AUC at the MRHD of 200 mg.

Reproductive and developmental toxicity

FREORLA had no effects on male fertility or spermatogenesis at doses up to 70 mg/kg/day at exposures equal to 26 times the unbound human AUC at the MRHD of 200 mg. FREORLA

resulted in effects on female fertility (lower fertility index, corpora lutea, and implantation sites) at exposures equal to 29 times the unbound human AUC at the MRHD of 200 mg and higher postimplantation loss in rats at exposures greater than or equal to 11 times the unbound human AUC at the MRHD of 200 mg. The effects on female fertility in rats reversed 1 month after cessation of FREORLA administration. No effects on female fertility were noted at exposures equal to 2 times the unbound human AUC at the MRHD of 200 mg.

No fetal malformations were observed in embryo-fetal development studies in rats or rabbits. In an embryo-fetal development study in pregnant rabbits, oral administration of FREORLA during gestation days 7 to 19 had no effects on embryo-fetal survival or fetal morphological development at exposures equal to 4 times the unbound human AUC at the MRHD of 200 mg. FREORLA resulted in an increase incidence of delayed ossification of the forelimb phalanges at exposures equal to 4 times the unbound human AUC at the MRHD of 200 mg.

In an embryo-fetal development study in pregnant rats, oral administration of FREORLA during gestation days 6 to 17 resulted in increased embryo-fetal lethality at exposures equal to 17 times the unbound human AUC at the MRHD of 200 mg. No embryo-fetal lethality was observed in pregnant rats orally dosed with FREORLA during organogenesis at exposures equal to 11 times the unbound human AUC at the MRHD of 200 mg. FREORLA resulted in increased incidences of skeletal variations of short 13th ribs at exposures greater than or equal to 11 times the unbound human AUC at the MRHD of 200 mg and reduced ventral processes, thickened ribs, and unossified metatarsals at exposures equal to 17 times the unbound human AUC at the MRHD of 200 mg. No skeletal variations were noted in rats at exposures equal to 2.4 times the unbound human AUC at the MRHD of 200 mg.

In a rat pre- and postnatal development study in pregnant rats, oral administration of FREORLA during gestation day 6 through lactation day 21 resulted in dystocia with prolonged parturition and lower offspring body weights at exposures greater than or equal to 11 times the unbound human AUC at the MRHD of 200 mg and lower postnatal survival at exposures equal to 17 times the unbound human AUC at the MRHD of 200 mg. No maternal or developmental toxicity was observed in either dams or offspring at exposures equal to 2.4 times the unbound human AUC at the MRHD of 200 mg.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

Tablet core

Microcrystalline cellulose
Dibasic calcium phosphate anhydrous
Sodium starch glycolate
Magnesium stearate

Film-coat

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

**6.2. Incompatibilities**

Not applicable.

**6.3. Shelf life**

30 months.

After reconstitution (for plastic bottle only) :
30 days after the packaging was opened.

**6.4. Special precautions for storage**

Store below 30ºC. Keep in original package.

**6.5. Nature and contents of container**

FREORLA 50 mg film-coated tablets

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

FREORLA 100 mg film-coated tablets

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

FREORLA 200 mg film-coated tablets

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

Not all pack sizes may be marketed.

**6.6. Special precautions for disposal and other handling**

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

## 7. MARKETING AUTHORISATION HOLDER

**Manufactured by:**
Pfizer Manufacturing Deutschland GmbH
Freiburg
Germany

**Imported by:**
PT. Pfizer Indonesia
Jakarta, Indonesia

## 8. MARKETING AUTHORISATION NUMBER(S)

FREORLA® 50 mg film-coated tablets, Box, 1 plastic bottle @ 30 film coated tablets; Reg. No.: DKXXXXXXXXXXX.
FREORLA® 100 mg film-coated tablets, Box, 1 plastic bottle @ 30 film coated tablets; Reg. No.: DKXXXXXXXXXXX.
FREORLA® 200 mg film-coated tablets, Box, 1 plastic bottle @ 30 film coated tablets; Reg. No.: DKXXXXXXXXXXX.

**HARUS DENGAN RESEP DOKTER**

## 9. DATE OF REVISION OF THE TEXT

12/2022

**LEAFLET KEMASAN: INFORMASI BAGI PENGGUNA**

**FREORLA® 50 mg tablet salut selaput**
**FREORLA® 100 mg tablet salut selaput**
**FREORLA® 200 mg tablet salut selaput**

**Abrocitinib**

**Baca isi leaflet ini dengan teliti sebelum Anda menggunakan obat ini karena berisi informasi penting untuk Anda.**
- Simpan leaflet ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker, atau perawat Anda.
- Obat ini telah diresepkan hanya untuk Anda. Jangan memberikannya kepada orang lain. Obat ini dapat membahayakan mereka, sekalipun tanda-tanda penyakit mereka sama dengan Anda.
- Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter, apoteker, atau perawat Anda. Termasuk setiap kemungkinan efek samping yang tidak tercantum dalam leaflet ini. Lihat bagian 13.

**Apa isi leaflet ini**


## 1. Nama obat

FREORLA®

## 2. Bentuk sediaan

Tablet salut selaput.

FREORLA 50 mg tablet salut selaput

Merah muda, tablet berbentuk oval dengan panjang 10.50 mm dan lebar 4.75 mm, terdapat deboss “PFE” pada salah satu sisi dan “ABR 50” pada sisi lainnya.


DISETUJUI OLEH BPOM: 11/01/2023

ID: EREG10024112100471,
EREG10024112100473,
EREG10024112100475

FREORLA 100 mg tablet salut selaput

Merah muda, tablet berbentuk lingkaran dengan diameter 9.00 mm, terdapat deboss “PFE” pada salah satu sisi dan “ABR 100” pada sisi lainnya.

FREORLA 200 mg tablet salut selaput

Merah muda, tablet berbentuk oval dengan panjang 18.42 mm dan lebar 8.00 mm dengan deboss “PFE” pada salah satu sisi dan “ABR 200” pada sisi lainnya.

**3. Deskripsi obat**

FREORLA® adalah obat yang berisi zat aktif abrocitinib.

FREORLA® adalah penghambat Janus kinase (JAK) 1, yang mengurangi peradangan dan gatal pada dermatitis atopik.

**4. Apa kandungan obat ini?**

FREORLA® 50 mg, 100 mg, atau 200 mg tablet salut selaput

- Zat aktifnya adalah abrocitinib.
  Masing-masing tablet mengandung 50 mg, 100 mg, atau 200 mg abrocitinib.
- Bahan lainnya adalah:

- Inti tablet: mikrokristalin selulosa, kalsium fosfat anhidrat dibasa, natrium pati glikolat, magnesium stearat.
- Salut selaput: hipromelosa (E464), titanium dioksida (E171), laktosa monohidrat, Makrogol, triasetin (E1518), besi merah oksida (E172).

**5. Kekuatan obat**

FREORLA® 50 mg, 100 mg, atau 200 mg tablet salut selaput

**6. Apa kegunaan obat ini?**

FREORLA® diindikasikan untuk pengobatan pasien dewasa yang berusia 18 tahun ke atas dengan dermatitis atopik sedang hingga berat, termasuk meredakan rasa gatal, pada pasien yang sebelumnya menunjukkan respon tidak adekuat terhadap pemberian terapi topikal yang diresepkan, atau pada mereka yang tidak disarankan untuk menerima terapi tersebut.

**7. Berapa banyak dan seberapa sering Anda seharusnya menggunakan obat ini? Apa yang harus dilakukan jika ada dosis yang terlewat?**

Selalu gunakan obat ini sesuai dengan petunjuk dokter Anda. Tanyakan kepada dokter atau apoteker jika Anda merasa tidak yakin.

FREORLA® adalah tablet yang diminum secara oral. Obat ini dapat digunakan dengan atau tanpa obat eksim kulit oles lainnya.

Dosis yang dianjurkan pada orang dewasa yang berusia 18 tahun keatas adalah 100 mg atau 200 mg satu kali sehari. Untuk sebagian besar pasien, dosis awal yang dianjurkan adalah 200 mg satu kali

sehari. Beberapa pasien memerlukan dosis awal yang lebih rendah. Dokter dapat memberi Anda dosis 100 mg satu kali sehari jika Anda berusia di atas 65 tahun, atau jika Anda memiliki riwayat kesehatan atau kondisi kesehatan tertentu.

Jika Anda memiliki masalah ginjal sedang hingga berat atau jika Anda juga mendapatkan resep obat tertentu lainnya, dosis awal dapat sebesar 50 mg atau 100 mg satu kali sehari. Anda akan mendapatkan dosis awal berdasarkan kebutuhan dan riwayat kesehatan Anda, dan oleh karena itu Anda harus meminum obat ini dengan tepat sesuai anjuran dokter Anda.

Dosis harian maksimum adalah 200 mg.

Setelah memulai pengobatan, dokter Anda dapat menyesuaikan dosisnya berdasarkan sejauh mana efektivitas obat serta efek samping yang Anda rasakan. Jika obat bekerja dengan baik, dosis dapat diturunkan. Pengobatan juga dapat dihentikan sementara waktu atau secara permanen jika hasil tes darah menunjukkan jumlah sel darah putih atau trombosit yang rendah.

Anda harus menelan tablet secara utuh menggunakan air. Jangan membagi, menggerus, atau mengunyah tablet sebelum ditelan.

Anda bisa meminum tablet sebelum atau sesudah makan. Jika Anda merasa ingin muntah (mual) saat meminum obat ini, sebaiknya Anda meminumnya sesudah makan. Untuk membantu Anda mengingat waktu meminum FREORLA®, disarankan untuk meminumnya pada waktu yang sama setiap hari.

**Jika Anda lupa meminum FREORLA®**

- Jika ada satu dosis yang terlewat, segera minum begitu Anda mengingatnya.
- Jika Anda terlupa dengan dosis Anda sepanjang hari, lewatkan dosis tersebut dan minum hanya dosis tunggal seperti biasa keesokan harinya.
- Jangan meminum dosis ganda untuk mengganti tablet yang terlewatkan.

**Jika Anda berhenti meminum FREORLA®**

Anda tidak boleh berhenti meminum FREORLA® tanpa berkonsultasi terlebih dahulu dengan dokter Anda. Dokter Anda yang akan memutuskan durasi pengobatan Anda dengan FREORLA®.

Jika Anda memiliki pertanyaan lebih lanjut seputar penggunaan obat ini, tanyakan kepada dokter atau apoteker Anda.

## 8. Apa yang harus dipertimbangkan saat meminum obat ini?

**Peringatan dan tindakan pencegahan**
Sebelum memulai penggunaan FREORLA®, beri tahu tenaga kesehatan Anda jika:
Anda mengalami infeksi (demam, berkeringat, atau menggigil, nyeri otot, batuk atau sesak napas, dahak berdarah, penurunan berat badan, diare dan sakit perut, rasa terbakar saat buang air kecil atau frekuensi buang air kecil melebihi normal, merasa sangat lelah) – FREORLA® dapat mengurangi kemampuan tubuh Anda untuk melawan infeksi, sehingga dapat memperburuk infeksi yang sudah Anda derita sebelumnya, atau membuat Anda lebih rentan untuk terkena infeksi baru

- Anda pernah terkena tuberkulosis atau telah melakukan kontak erat dengan seorang penderita tuberkulosis. Dokter Anda akan melakukan tes apakah Anda menderita tuberkulosis sebelum memulai pengobatan dengan FREORLA® dan dapat melakukan tes kembali selama pengobatan berlangsung

- Anda pernah menderita penyakit herpes zoster, karena FREORLA® dapat menyebabkannya kekambuhan. Beri tahu dokter Anda jika Anda mengalami ruam kulit yang nyeri disertai lepuh sebab bisa jadi menandakan Anda terkena penyakit herpes
- Anda pernah menderita hepatitis B atau hepatitis C
- Organ hati Anda tidak bekerja sebagaimana mestinya
- Anda sedang hamil atau menyusui (lihat bagian 11. Apakah obat tersebut aman bagi ibu hamil dan menyusui?).
- Anda baru saja menjalani atau berencana untuk melakukan vaksinasi (imunisasi)–karena vaksin hidup tidak dianjurkan selama Anda menggunakan FREORLA®
- Anda pernah memiliki bekuan darah pada pembuluh vena kaki Anda (trombosis vena dalam) atau paru-paru (emboli paru). Beri tahu dokter Anda jika Anda mengalami pembengkakan pada kaki yang terasa nyeri, nyeri dada, atau sesak napas, sebab ini bisa jadi menandakan adanya bekuan darah dalam pembuluh vena
- mengalami kenaikan kadar kolesterol darah atau kondisi kesehatan lainnya yang membuat Anda lebih rentan mengalami penyakit jantung–belum jelas apakah FREORLA® meningkatkan risiko penyakit jantung.Dokter anda akan berdiskusi bersama Anda apakah pengobatan menggunakan obat ini sudah sesuai atau jika Anda memerlukan pemeriksaan tambahan saat meminum obat ini.
- Anda menderita kanker atau pernah menderita kanker apa pun–karena dokter Anda harus memutuskan apakah Anda tetap dapat menjalani pengobatan dengan FREORLA®.

Tes pemantauan tambahan
Dokter Anda akan melakukan tes darah sebelum dan selama pengobatan dengan FREORLA® dan dapat menyesuaikan pengobatan Anda jika diperlukan.

**FREORLA® mengandung natrium**
Obat ini mengandung kurang dari 1 mmol natrium (23 mg) per tablet, sehingga FREORLA® pada dasarnya bisa dikatakan ‘bebas natrium’.

**FREORLA® mengandung laktosa**
Jika Anda telah diberi tahu oleh dokter bahwa Anda mempunyai intoleransi terhadap jenis gula tertentu, hubungi dokter Anda sebelum meminum obat ini.

## 9. Apa saja obat lain atau makanan yang harus dihindari selama menggunakan obat ini?

Beri tahu dokter atau apoteker Anda jika Anda sedang meminum, baru-baru ini meminum, atau mungkin meminum obat-obatan lain.

Secara khusus, beri tahu dokter atau apoteker Anda sebelum meminum FREORLA® jika Anda sedang mengonsumsi obat-obatan untuk mengobati:

- infeksi jamur (seperti flukonazol), depresi (seperti fluoxetine atau fluvoksamin), stroke (seperti ticlopidine), karena dapat meningkatkan efek samping FREORLA®.
- -acidreflux perut (seperti antacid, famotidine atau omeprazole), karena mereka mungkin mengurangi jumlah FREORLA® dalam darahmu.
- depresi (seperti bupropion, duloxetine), gangguan tidur (seperti ramelteon), serangan (seperti S-mephenytoin), sindrom iritasi usus (seperti alosetron), spasme otot (seperti tizanidine), karena FREORLA® dapat mengubah jumlah obat-obatan ini dalam darahmu.
- gagal jantung (seperti digoksin) atau stroke (seperti dabigatran), karena FREORLA® dapat meningkatkan efeknya.
- asma, artritis reumatoid, atau dermatitis atopik (seperti terapi antibodi biologis, obat yang mengendalikan respon imun tubuh seperti siklosporin, inhibitor Janus kinase lainnya, seperti baricitinib, upadacitinib), karena mereka dapat meningkatkan resiko efek samping.

Dokter Anda dapat memberi tahu Anda untuk menghindari penggunaan atau berhenti meminum FREORLA® jika Anda sedang mengonsumsi obat-obatan untuk mengobati:
- tuberkulosis (seperti rifampisin) karena dapat mengurangi efektivitas kerja FREORLA®.

Jika ada salah satu dari yang di atas sesuai dengan kondisi Anda atau Anda masih ragu, konsultasikan dengan dokter atau apoteker sebelum menggunakan FREORLA®.

**10. Apakah obat tersebut aman bagi ibu hamil dan menyusui?**

Kehamilan
Jika Anda sedang hamil atau menyusui, memiliki kemungkinan atau rencana untuk hamil, mintalah saran dari dokter atau apoteker Anda sebelum menggunakan obat ini.

Kontrasepsi pada perempuan
Jika Anda adalah perempuan dalam masa produktif, Anda harus menggunakan metode kontrasepsi yang efektif untuk menghindari kehamilan selama menjalani pengobatan dengan FREORLA® dan selama setidaknya 1 bulan setelah dosis pengobatan Anda yang terakhir. Anda harus memberi tahu dokter jika Anda hamil karena FREORLA® tidak boleh digunakan selama kehamilan kecuali jika benar-benar dibutuhkan.

Kehamilan
Jangan menggunakan FREORLA® jika Anda sedang hamil, menduga diri Anda sedang hamil, atau berencana untuk hamil karena dapat membahayakan janin. Beri tahu dokter Anda segera jika kemudian Anda hamil atau menduga Anda mungkin hamil selama pengobatan.

Menyusui
Jangan menggunakan FREORLA® selama menyusui sebab belum diketahui apakah obat ini dikeluarkan bersama ASI dan berdampak terhadap bayi. Anda dan dokter Anda harus menentukan apakah Anda akan menyusui atau menggunakan obat ini.

Kesuburan
FREORLA® dapat menyebabkan penurunan kesuburan sementara pada perempuan dalam masa produktif. Efek ini dapat mereda setelah pengobatan dihentikan.

**11. Apakah pasien diizinkan mengemudi dan mengoperasikan mesin saat menggunakan obat ini?**

FREORLA® tidak memengaruhi kemampuan dalam mengemudi atau mengoperasikan mesin.

**12. Apa saja potensi efek yang tidak diinginkan dari penggunaan obat ini?**

Seperti semua obat-obatan yang ada, obat ini bisa menimbulkan efek samping, meskipun tidak semua orang mengalaminya.

Sebagian dapat bersifat serius dan memerlukan penanganan medis.

**Efek samping serius**

Efek samping serius bersifat tidak umum (dapat dialami hingga 1 di antara 100 orang).

Konsultasikan dengan dokter Anda atau dapatkan pertolongan medis segera jika Anda menunjukkan tanda-tanda berupa:

- Penyakit herpes (herpes zoster), ruam kulit nyeri yang disertai lepuh dan demam
- Bekuan darah di paru-paru, kaki, atau pelvis dengan gejala berupa pembengkakan pada kaki yang terasa nyeri, nyeri dada, atau sesak napas

**Sangat umum** (dapat dialami lebih dari 1 di antara 10 orang)
Perut terasa tidak nyaman (mual)

**Umum** (dapat dialami 1 di antara 10 orang)
- Cold sore dan jenis infeksi herpes simpleks lainnya
- Muntah
- Nyeri perut atas
- Sakit kepala
- Pusing
- Jerawat
- Peningkatan enzim kreatin fosfokinase, yang ditunjukkan melalui tes darah

**Tidak Umum** (dapat dialami 1 di antara 100 orang)
- Pneumonia (infeksi paru)
- Kadar trombosit rendah (fragmen sel yang terlibat dalam pembekuan), ditunjukkan melalui tes darah
- Kadar limfosit rendah (sejenis sel darah putih), ditunjukkan melalui tes darah
- Kadar kolesterol darah tinggi (sejenis lemak dalam darah), ditunjukkan melalui tes darah

**Melaporkan efek samping**
Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter, apoteker, atau perawat Anda. Termasuk setiap kemungkinan efek samping yang tidak tercantum dalam leaflet ini. Dengan melaporkan efek samping, Anda bisa membantu memberikan informasi lebih lanjut mengenai keamanan obat ini.

## 13. Tanda-tanda dan gejala-gejala kelebihan dosis

Belum ada pengalaman kelebihan dosis dalam penggunaan FREORLA®. Belum ada antidot spesifik untuk kelebihan dosis dalam penggunaan FREORLA®. Jika terjadi kelebihan dosis, disarankan agar pasien dipantau untuk melihat tanda-tanda dan gejala-gejala reaksi merugikan. Pengobatan ditujukan untuk mengatasi gejala dan bersifat pendukung.

## 14. Apa yang harus dilakukan jika Anda menggunakan lebih dari dosis yang dianjurkan?

Jika Anda menggunakan FREORLA® melebihi dosis yang semestinya, hubungi dokter Anda. Anda mungkin mengalami beberapa efek samping yang diuraikan dalam bagian 13.

## 15. Bagaimana cara menyimpan obat ini?

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Simpan di bawah suhu 30˚C. Simpan dalam kemasan asli.

Waktu kedaluwarsa:
30 bulan.

Jangan menggunakan obat ini setelah tanggal kedaluwarsa yang tertera pada label setelah tulisan EXP. Tanggal kedaluwarsa mengacu pada hari terakhir dari bulan yang tertera.

Produk ini tidak memiliki batasan penyimpanan khusus.

Jangan buang obat melalui saluran pembuangan air atau bersama sampah rumah tangga. Tanyakan kepada apoteker cara membuang obat yang sudah tidak digunakan lagi. Langkah-langkah ini akan membantu melindungi lingkungan.

**16. Nomor otorisasi pemasaran**

FREORLA® 50 mg tablet salut selaput, Dus, 2 blister @ 7 tablet salut selaput; No. Reg.: DKXXXXXXXXXXX.
FREORLA® 100 mg tablet salut selaput, Dus, 2 blister @ 7 tablet salut selaput; No. Reg.: DKXXXXXXXXXXX.
FREORLA® 200 mg tablet salut selaput, Dus, 2 blister @ 7 tablet salut selaput; No. Reg.: DKXXXXXXXXXXX.

**17. Nama dan alamat pemohon dan/atau pemilik obat sesuai dengan ketentuan yang berlaku**

**Diproduksi oleh:**
Pfizer Manufacturing Deutschland GmbH
Freiburg
Jerman

**Diimpor oleh:**
PT. Pfizer Indonesia
Jakarta, Indonesia

**18. Tanggal revisi**
12/2022

**19. Peringatan khusus**

**HARUS DENGAN RESEP DOKTER**

**LEAFLET KEMASAN: INFORMASI BAGI PENGGUNA**

**FREORLA® 50 mg tablet salut selaput**
**FREORLA® 100 mg tablet salut selaput**
**FREORLA® 200 mg tablet salut selaput**

**Abrocitinib**

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- Obat ini telah diresepkan hanya untuk Anda. Jangan memberikannya kepada orang lain. Obat ini dapat membahayakan mereka, sekalipun tanda-tanda penyakit mereka sama dengan Anda.
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**Apa isi leaflet ini**


## 1. Nama obat

FREORLA®

## 2. Bentuk sediaan

Tablet salut selaput.

FREORLA 50 mg tablet salut selaput

Merah muda, tablet berbentuk oval dengan panjang 10.50 mm dan lebar 4.75 mm, terdapat deboss “PFE” pada salah satu sisi dan “ABR 50” pada sisi lainnya.

FREORLA 100 mg tablet salut selaput

Merah muda, tablet berbentuk lingkaran dengan diameter 9.00 mm, terdapat deboss “PFE” pada salah satu sisi dan “ABR 100” pada sisi lainnya.

FREORLA 200 mg tablet salut selaput

Merah muda, tablet berbentuk oval dengan panjang 18.42 mm dan lebar 8.00 mm dengan deboss “PFE” pada salah satu sisi dan “ABR 200” pada sisi lainnya.

**3. Deskripsi obat**

FREORLA® adalah obat yang berisi zat aktif abrocitinib.

FREORLA® adalah penghambat Janus kinase (JAK) 1, yang mengurangi peradangan dan gatal pada dermatitis atopik.

**4. Apa kandungan obat ini?**

FREORLA® 50 mg, 100 mg, atau 200 mg tablet salut selaput

- Zat aktifnya adalah abrocitinib.
  Masing-masing tablet mengandung 50 mg, 100 mg, atau 200 mg abrocitinib.
- Bahan lainnya adalah:

- Inti tablet: mikrokristalin selulosa, kalsium fosfat anhidrat dibasa, natrium pati glikolat, magnesium stearat.
- Salut selaput: hipromelosa (E464), titanium dioksida (E171), laktosa monohidrat, Makrogol, triasetin (E1518), besi merah oksida (E172).

**5. Kekuatan obat**

FREORLA® 50 mg, 100 mg, atau 200 mg tablet salut selaput

**6. Apa kegunaan obat ini?**

FREORLA® diindikasikan untuk pengobatan pasien dewasa yang berusia 18 tahun ke atas dengan dermatitis atopik sedang hingga berat, termasuk meredakan rasa gatal, pada pasien yang sebelumnya menunjukkan respon tidak adekuat terhadap pemberian terapi topikal yang diresepkan, atau pada mereka yang tidak disarankan untuk menerima terapi tersebut.

**7. Berapa banyak dan seberapa sering Anda seharusnya menggunakan obat ini? Apa yang harus dilakukan jika ada dosis yang terlewat?**

Selalu gunakan obat ini sesuai dengan petunjuk dokter Anda. Tanyakan kepada dokter atau apoteker jika Anda merasa tidak yakin.

FREORLA® adalah tablet yang diminum secara oral. Obat ini dapat digunakan dengan atau tanpa obat eksim kulit oles lainnya.

Dosis yang dianjurkan pada orang dewasa yang berusia 18 tahun keatas adalah 100 mg atau 200 mg satu kali sehari. Untuk sebagian besar pasien, dosis awal yang dianjurkan adalah 200 mg satu kali

sehari. Beberapa pasien memerlukan dosis awal yang lebih rendah. Dokter dapat memberi Anda dosis 100 mg satu kali sehari jika Anda berusia di atas 65 tahun, atau jika Anda memiliki riwayat kesehatan atau kondisi kesehatan tertentu.

Jika Anda memiliki masalah ginjal sedang hingga berat atau jika Anda juga mendapatkan resep obat tertentu lainnya, dosis awal dapat sebesar 50 mg atau 100 mg satu kali sehari. Anda akan mendapatkan dosis awal berdasarkan kebutuhan dan riwayat kesehatan Anda, dan oleh karena itu Anda harus meminum obat ini dengan tepat sesuai anjuran dokter Anda.

Dosis harian maksimum adalah 200 mg.

Setelah memulai pengobatan, dokter Anda dapat menyesuaikan dosisnya berdasarkan sejauh mana efektivitas obat serta efek samping yang Anda rasakan. Jika obat bekerja dengan baik, dosis dapat diturunkan. Pengobatan juga dapat dihentikan sementara waktu atau secara permanen jika hasil tes darah menunjukkan jumlah sel darah putih atau trombosit yang rendah.

Anda harus menelan tablet secara utuh menggunakan air. Jangan membagi, menggerus, atau mengunyah tablet sebelum ditelan.

Anda bisa meminum tablet sebelum atau sesudah makan. Jika Anda merasa ingin muntah (mual) saat meminum obat ini, sebaiknya Anda meminumnya sesudah makan. Untuk membantu Anda mengingat waktu meminum FREORLA®, disarankan untuk meminumnya pada waktu yang sama setiap hari.

**Jika Anda lupa meminum FREORLA®**

- Jika ada satu dosis yang terlewat, segera minum begitu Anda mengingatnya.
- Jika Anda terlupa dengan dosis Anda sepanjang hari, lewatkan dosis tersebut dan minum hanya dosis tunggal seperti biasa keesokan harinya.
- Jangan meminum dosis ganda untuk mengganti tablet yang terlewatkan.

**Jika Anda berhenti meminum FREORLA®**

Anda tidak boleh berhenti meminum FREORLA® tanpa berkonsultasi terlebih dahulu dengan dokter Anda. Dokter Anda yang akan memutuskan durasi pengobatan Anda dengan FREORLA®.

Jika Anda memiliki pertanyaan lebih lanjut seputar penggunaan obat ini, tanyakan kepada dokter atau apoteker Anda.

## 8. Apa yang harus dipertimbangkan saat meminum obat ini?

**Peringatan dan tindakan pencegahan**
Sebelum memulai penggunaan FREORLA®, beri tahu tenaga kesehatan Anda jika:
Anda mengalami infeksi (demam, berkeringat, atau menggigil, nyeri otot, batuk atau sesak napas, dahak berdarah, penurunan berat badan, diare dan sakit perut, rasa terbakar saat buang air kecil atau frekuensi buang air kecil melebihi normal, merasa sangat lelah) – FREORLA® dapat mengurangi kemampuan tubuh Anda untuk melawan infeksi, sehingga dapat memperburuk infeksi yang sudah Anda derita sebelumnya, atau membuat Anda lebih rentan untuk terkena infeksi baru

- Anda pernah terkena tuberkulosis atau telah melakukan kontak erat dengan seorang penderita tuberkulosis. Dokter Anda akan melakukan tes apakah Anda menderita tuberkulosis sebelum memulai pengobatan dengan FREORLA® dan dapat melakukan tes kembali selama pengobatan berlangsung

- Anda pernah menderita penyakit herpes zoster, karena FREORLA® dapat menyebabkannya kekambuhan. Beri tahu dokter Anda jika Anda mengalami ruam kulit yang nyeri disertai lepuh sebab bisa jadi menandakan Anda terkena penyakit herpes
- Anda pernah menderita hepatitis B atau hepatitis C
- Organ hati Anda tidak bekerja sebagaimana mestinya
- Anda sedang hamil atau menyusui (lihat bagian 11. Apakah obat tersebut aman bagi ibu hamil dan menyusui?).
- Anda baru saja menjalani atau berencana untuk melakukan vaksinasi (imunisasi)–karena vaksin hidup tidak dianjurkan selama Anda menggunakan FREORLA®
- Anda pernah memiliki bekuan darah pada pembuluh vena kaki Anda (trombosis vena dalam) atau paru-paru (emboli paru). Beri tahu dokter Anda jika Anda mengalami pembengkakan pada kaki yang terasa nyeri, nyeri dada, atau sesak napas, sebab ini bisa jadi menandakan adanya bekuan darah dalam pembuluh vena
- mengalami kenaikan kadar kolesterol darah atau kondisi kesehatan lainnya yang membuat Anda lebih rentan mengalami penyakit jantung–belum jelas apakah FREORLA® meningkatkan risiko penyakit jantung.Dokter anda akan berdiskusi bersama Anda apakah pengobatan menggunakan obat ini sudah sesuai atau jika Anda memerlukan pemeriksaan tambahan saat meminum obat ini.
- Anda menderita kanker atau pernah menderita kanker apa pun–karena dokter Anda harus memutuskan apakah Anda tetap dapat menjalani pengobatan dengan FREORLA®.

Tes pemantauan tambahan
Dokter Anda akan melakukan tes darah sebelum dan selama pengobatan dengan FREORLA® dan dapat menyesuaikan pengobatan Anda jika diperlukan.

**FREORLA® mengandung natrium**
Obat ini mengandung kurang dari 1 mmol natrium (23 mg) per tablet, sehingga FREORLA® pada dasarnya bisa dikatakan ‘bebas natrium’.

**FREORLA® mengandung laktosa**
Jika Anda telah diberi tahu oleh dokter bahwa Anda mempunyai intoleransi terhadap jenis gula tertentu, hubungi dokter Anda sebelum meminum obat ini.

## 9. Apa saja obat lain atau makanan yang harus dihindari selama menggunakan obat ini?

Beri tahu dokter atau apoteker Anda jika Anda sedang meminum, baru-baru ini meminum, atau mungkin meminum obat-obatan lain.

Secara khusus, beri tahu dokter atau apoteker Anda sebelum meminum FREORLA® jika Anda sedang mengonsumsi obat-obatan untuk mengobati:

- infeksi jamur (seperti flukonazol), depresi (seperti fluoxetine atau fluvoksamin), stroke (seperti ticlopidine), karena dapat meningkatkan efek samping FREORLA®.
- -acidreflux perut (seperti antacid, famotidine atau omeprazole), karena mereka mungkin mengurangi jumlah FREORLA® dalam darahmu.
- depresi (seperti bupropion, duloxetine), gangguan tidur (seperti ramelteon), serangan (seperti S-mephenytoin), sindrom iritasi usus (seperti alosetron), spasme otot (seperti tizanidine), karena FREORLA® dapat mengubah jumlah obat-obatan ini dalam darahmu.
- gagal jantung (seperti digoksin) atau stroke (seperti dabigatran), karena FREORLA® dapat meningkatkan efeknya.
- asma, artritis reumatoid, atau dermatitis atopik (seperti terapi antibodi biologis, obat yang mengendalikan respon imun tubuh seperti siklosporin, inhibitor Janus kinase lainnya, seperti baricitinib, upadacitinib), karena mereka dapat meningkatkan resiko efek samping.

Dokter Anda dapat memberi tahu Anda untuk menghindari penggunaan atau berhenti meminum FREORLA® jika Anda sedang mengonsumsi obat-obatan untuk mengobati:
- tuberkulosis (seperti rifampisin) karena dapat mengurangi efektivitas kerja FREORLA®.

Jika ada salah satu dari yang di atas sesuai dengan kondisi Anda atau Anda masih ragu, konsultasikan dengan dokter atau apoteker sebelum menggunakan FREORLA®.

**10. Apakah obat tersebut aman bagi ibu hamil dan menyusui?**

Kehamilan
Jika Anda sedang hamil atau menyusui, memiliki kemungkinan atau rencana untuk hamil, mintalah saran dari dokter atau apoteker Anda sebelum menggunakan obat ini.

Kontrasepsi pada perempuan
Jika Anda adalah perempuan dalam masa produktif, Anda harus menggunakan metode kontrasepsi yang efektif untuk menghindari kehamilan selama menjalani pengobatan dengan FREORLA® dan selama setidaknya 1 bulan setelah dosis pengobatan Anda yang terakhir. Anda harus memberi tahu dokter jika Anda hamil karena FREORLA® tidak boleh digunakan selama kehamilan kecuali jika benar-benar dibutuhkan.

Kehamilan
Jangan menggunakan FREORLA® jika Anda sedang hamil, menduga diri Anda sedang hamil, atau berencana untuk hamil karena dapat membahayakan janin. Beri tahu dokter Anda segera jika kemudian Anda hamil atau menduga Anda mungkin hamil selama pengobatan.

Menyusui
Jangan menggunakan FREORLA® selama menyusui sebab belum diketahui apakah obat ini dikeluarkan bersama ASI dan berdampak terhadap bayi. Anda dan dokter Anda harus menentukan apakah Anda akan menyusui atau menggunakan obat ini.

Kesuburan
FREORLA® dapat menyebabkan penurunan kesuburan sementara pada perempuan dalam masa produktif. Efek ini dapat mereda setelah pengobatan dihentikan.

**11. Apakah pasien diizinkan mengemudi dan mengoperasikan mesin saat menggunakan obat ini?**

FREORLA® tidak memengaruhi kemampuan dalam mengemudi atau mengoperasikan mesin.

**12. Apa saja potensi efek yang tidak diinginkan dari penggunaan obat ini?**

Seperti semua obat-obatan yang ada, obat ini bisa menimbulkan efek samping, meskipun tidak semua orang mengalaminya.

Sebagian dapat bersifat serius dan memerlukan penanganan medis.

**Efek samping serius**

Efek samping serius bersifat tidak umum (dapat dialami hingga 1 di antara 100 orang).

Konsultasikan dengan dokter Anda atau dapatkan pertolongan medis segera jika Anda menunjukkan tanda-tanda berupa:

- Penyakit herpes (herpes zoster), ruam kulit nyeri yang disertai lepuh dan demam
- Bekuan darah di paru-paru, kaki, atau pelvis dengan gejala berupa pembengkakan pada kaki yang terasa nyeri, nyeri dada, atau sesak napas

**Sangat umum** (dapat dialami lebih dari 1 di antara 10 orang)
Perut terasa tidak nyaman (mual)

**Umum** (dapat dialami 1 di antara 10 orang)
- Cold sore dan jenis infeksi herpes simpleks lainnya
- Muntah
- Nyeri perut atas
- Sakit kepala
- Pusing
- Jerawat
- Peningkatan enzim kreatin fosfokinase, yang ditunjukkan melalui tes darah

**Tidak Umum** (dapat dialami 1 di antara 100 orang)
- Pneumonia (infeksi paru)
- Kadar trombosit rendah (fragmen sel yang terlibat dalam pembekuan), ditunjukkan melalui tes darah
- Kadar limfosit rendah (sejenis sel darah putih), ditunjukkan melalui tes darah
- Kadar kolesterol darah tinggi (sejenis lemak dalam darah), ditunjukkan melalui tes darah

**Melaporkan efek samping**
Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter, apoteker, atau perawat Anda. Termasuk setiap kemungkinan efek samping yang tidak tercantum dalam leaflet ini. Dengan melaporkan efek samping, Anda bisa membantu memberikan informasi lebih lanjut mengenai keamanan obat ini.

## 13. Tanda-tanda dan gejala-gejala kelebihan dosis

Belum ada pengalaman kelebihan dosis dalam penggunaan FREORLA®. Belum ada antidot spesifik untuk kelebihan dosis dalam penggunaan FREORLA®. Jika terjadi kelebihan dosis, disarankan agar pasien dipantau untuk melihat tanda-tanda dan gejala-gejala reaksi merugikan. Pengobatan ditujukan untuk mengatasi gejala dan bersifat pendukung.

## 14. Apa yang harus dilakukan jika Anda menggunakan lebih dari dosis yang dianjurkan?

Jika Anda menggunakan FREORLA® melebihi dosis yang semestinya, hubungi dokter Anda. Anda mungkin mengalami beberapa efek samping yang diuraikan dalam bagian 13.

## 15. Bagaimana cara menyimpan obat ini?

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Simpan di bawah suhu 30˚C. Simpan dalam kemasan asli.

Waktu kedaluwarsa:
30 bulan.

Jangan menggunakan obat ini setelah tanggal kedaluwarsa yang tertera pada label setelah tulisan EXP. Tanggal kedaluwarsa mengacu pada hari terakhir dari bulan yang tertera.

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Produk ini tidak memiliki batasan penyimpanan khusus.

Jangan buang obat melalui saluran pembuangan air atau bersama sampah rumah tangga. Tanyakan kepada apoteker cara membuang obat yang sudah tidak digunakan lagi. Langkah-langkah ini akan membantu melindungi lingkungan.

Setelah rekonstitusi :
30 hari setelah kemasan dibuka.

**16. Nomor otorisasi pemasaran**

FREORLA® 50 mg tablet salut selaput, Dus, 1 botol plastik @ 30 tablet salut selaput; No. Reg.: DKXXXXXXXXXXX.
FREORLA® 100 mg tablet salut selaput, Dus, 1 botol plastik @ 30 tablet salut selaput; No. Reg.: DKXXXXXXXXXXX.
FREORLA® 200 mg tablet salut selaput, Dus, 1 botol plastik @ 30 tablet salut selaput; No. Reg.: DKXXXXXXXXXXX.

**17. Nama dan alamat pemohon dan/atau pemilik obat sesuai dengan ketentuan yang berlaku**

**Diproduksi oleh:**
Pfizer Manufacturing Deutschland GmbH
Freiburg
Jerman

**Diimpor oleh:**
PT. Pfizer Indonesia
Jakarta, Indonesia

**18. Tanggal revisi**
12/2022

**19. Peringatan khusus**

**HARUS DENGAN RESEP DOKTER**