Date: 27 June 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

CIBINQO

International non-proprietary name: abrocitinib
Pharmaceutical form: film-coated tablet
Dosage strength(s): 100 mg, 50 mg
Route(s) of administration: oral
Marketing Authorisation Holder: Pfizer AG
Marketing Authorisation No.: 68174
Decision and Decision date: approved on 5 April 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

AD	Atopic dermatitis
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
CYP	Cytochrome P450
DDI	Drug-drug interaction
EASI	Eczema Area and Severity Index
EMA	European Medicines Agency
EPO	Erythropoietin
ERA	Environmental Risk Assessment
ESRD	End-stage renal disease
FDA	U.S. Food and Drug Administration
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
IFN	Interferon
Ig	Immunoglobulin
IGA	Investigator's Global Assessment 5-point scale (0= clear - 4= severe)
IL	Interleukin
INN	International nonproprietary name
ITT	Intention-to-treat
IV	Intravenous
JAK	Janus kinase
LoQ	List of Questions
MAH	Marketing Authorisation Holder
MAO	Monoamine oxidase
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
NRI	Non-responder imputation
NRS	Numeric Rating Scale; 0-10
OAT	Organic anion transporter
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PDE4	Phosphodiesterase type 4
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PO	Per os
PopPK	Population pharmacokinetics
PP-NRS	Peak Pruritus Numerical Rating Scale

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PSAAD	Pruritus and Symptoms Assessment for AD: arithmetic mean of 11 items (0 -10)
PSP	Pediatric Study Plan (US-FDA)
QD	Once daily
RMP	Risk Management Plan
SAE	Serious adverse event
SCORAD	SCORing Atopic Dermatitis
STAT	Signal transducer and activator of transcription
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
TYK2	Tyrosine kinase 2

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance abrocitinib of the medicinal product mentioned above.

Work-sharing procedure
The applicant requested a work-sharing procedure with Singapore.
The Access NAS (New Active Substance) work-sharing initiative is a collaboration between regulatory authorities, i.e. Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA), Swissmedic, and the pharmaceutical industry.
The work-sharing initiative coordinates the assessment of an NAS application that has been filed in at least two jurisdictions.

2.2 Indication and Dosage

2.2.1 Requested Indication

TRADENAME is used to treat moderate to severe atopic dermatitis in adults and patients 12 years of age and older who are candidates for systemic therapy.

2.2.2 Approved Indication

Cibinqo is indicated for the treatment of moderate to severe atopic dermatitis in adults when therapy with topical medications does not provide adequate disease control or cannot be used.

2.2.3 Requested Dosage

Summary of the applied standard dosage:

The recommended dose of abrocitinib is 100 mg or 200 mg once daily, based on the individual goal of the therapy and potential risk of adverse reactions.
Abrocitinib may be used as a monotherapy or in combination with topical therapies.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	3 November 2020
Formal control completed	26 November 2020
List of Questions (LoQ)	1 April 2021
Answers to LoQ	30 May 2021
Predecision	20 August 2021
Answers to Predecision	27 September 2021
Labelling corrections	16 November 2021
Answers to Labelling corrections	16 December 2021
Final Decision	5 April 2022
Decision	approval

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3 Medical Context

Atopic dermatitis (AD) is a common disease (affecting up to 20% of children and 8% of adults). It is defined in different ways and may not necessarily constitute a single disease entity. The pathogenesis of AD is multifactorial, and barrier abnormalities of the skin and immunological factors play important roles. Atopic dermatitis is diagnosed on the basis of clinical criteria (primarily those proposed by Hanifin and Rajka). Various scores are commonly used for determining its severity, including SCORAD and EASI.

Most cases involve mild forms that can be well controlled with simple measures and topical treatment. However, severe, recalcitrant forms also exist which can require costly and, in some cases, potentially burdensome systemic treatments. For these reasons, the relevant guidelines recommend staged treatments.

Systemic treatments currently authorised in Switzerland are IL-4/IL-13 receptor inhibitors, JAK inhibitors and Cyclosporine.

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4 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's Request / Work-sharing procedure).

5 Nonclinical Aspects

5.1 Pharmacology

Abrocitinib is a selective inhibitor of Janus kinase (JAK) 1. It showed biochemical selectivity for JAK1 over the other JAK isoforms JAK2 (28-fold), JAK3 (>340-fold), and TYK2 (43-fold).

Abrocitinib metabolites M1 and M2 were more potent against JAK1 (IC_{50} of 43.4 nM and 17.9 nM) than JAK2 (IC_{50} 1,140 nM and 886 nM) or TYK2 (IC_{50} of 3,190 nM and 1,210 nM), and had little potency for JAK3 (IC_{50} >10,000 nM for both metabolites).

In cellular assays, abrocitinib was less potent against JAK1-independent signalling pathways when compared to JAK1-dependent signalling pathways in peripheral blood mononuclear cells and CD34+ progenitor cells, as well as in whole blood. The compound showed activity against interleukin (IL)-4, IL-13, IL-22 and IL-31-induced phosphorylation of signal transducers and activators of transcription (STATs) in whole blood, primary keratinocytes, primary intestinal epithelial cells, HT-29 cells and THP-1 cells. M1 and M2 were more potent against cytokines that transduce their signals via JAK1-dependent pathways, such as IFNα, IFNγ, IL-6, IL-10, IL-15, IL-21 and IL-27, than against cytokines that transduce their signals via JAK1-independent pathways, such as IL-12, IL-23 and EPO.

Abrocitinib inhibited trombopoietin (TPO)-induced phosphorylated (p)STAT5 and IL-6-induced pSTAT3 in megakaryocyte precursor cells and showed weak or little activity on the clearance of TPO by human platelets. These data correlate with the decrease in platelets observed in toxicity studies in rats.

The anti-inflammatory effects of abrocitinib were investigated in a rat arthritis model after daily oral administration of up to 50 mg/kg for 7 days. Dose-dependent inhibition of paw swelling was observed, as well as inhibition of cytokine (IL-6, IL-21 and IFNγ)-dependent STAT phosphorylation in *ex vivo* stimulated whole blood.

Studies on secondary pharmacodynamics showed that abrocitinib was an inhibitor of MAO-A, with an IC_{50} value 6.1-fold the unbound human C_{max}, but not an inhibitor of MAO-B. Considering the low distribution of abrocitinib to the brain, the safety factor of 6, as well as the reversibility of the inhibition, the risk of a potential inhibition of MAO-A by abrocitinib at clinically relevant levels is low.

The applicant conducted safety pharmacology studies to investigate potential effects on the cardiovascular, respiratory and central nervous system (CNS). The IC_{50} value for inhibition of the hERG channel was 94.7 µM. Considering the levels of unbound drug at the clinical dose (1.3 µM), it is unlikely that abrocitinib affects heart repolarisation.

In conscious telemetered monkeys administered abrocitinib at single oral doses of up to 150 mg/kg, increases in heart rate, decreases in respiratory rate consistent with heart rate changes and secondary decreases in PR-interval and QT-interval were observed at ≥15 mg/kg. Diastolic blood pressure was increased at 150 mg/kg.

The C_{max} value at 15 mg/kg corresponded to 0.9-fold the unbound human C_{max} at the therapeutic dose. There was no indication of QT-prolongation. No prolongation in cardiac repolarisation was observed in a thorough QT/QTc clinical study.

Regarding the CNS system, significant decreases in locomotor activity were observed at ≥75 mg/kg at a C_{max} value 10-fold the unbound human $C_{max.}$ Headache and dizziness were observed clinically.

Single oral doses of up to 600 mg/kg in rats did not exert any effects on respiratory function.

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5.2 Pharmacokinetics

The pharmacokinetics of abrocitinib was investigated after single i.v. and oral administration as well as after repeated oral administration in mice, rabbits, rats and cynomolgus monkeys. The PK profiles of the metabolites M1, M2 and M4 were studied in rats after repeated oral administration.

Abrocitinib was rapidly absorbed in rats and monkeys following a single 3 mg/kg oral administration with T_{max} reached at 0.5 hours. In humans, T_{max} varied from 0.5 to 1 hour. The oral bioavailability differed consistently between rats (95.6%), monkeys (9.8%) and humans (60%).

Volume of distribution was similar in rats, monkeys and humans, which suggests extensive distribution to the organs and tissues. $T_{1/2}$ in rats and monkeys (0.8 and 0.5 hours) was shorter than in humans (2 to 5 hours). Blood clearance was also higher in rats and monkeys (26.6 mL/min/kg and 30.8 mL/min/kg) compared to humans (12.1 mL/min/kg).

In mouse, rat, rabbit and monkey repeat-dose toxicity studies, abrocitinib exposure (C_{max} and AUC_{24}) increased with increasing dose. In mice, rats and monkeys, there were no sex-related differences or accumulation.

In a tissue distribution study with oral administration of 10 mg/kg ^{14}C-abrocitinib to pigmented rats, extensive distribution of drug-derived radioactivity was observed in most tissues. The liver, uveal tract, kidneys, adrenal glands and salivary glands had the highest concentrations of radioactivity. The drug-derived radioactivity present in the uveal tract shows an affinity for melanin; this association was slowly reversible. Abrocitinib showed limited distribution to the CNS.

Abrocitinib plasma protein binding was similar in rats, monkeys and humans (62%, 63% and 64%, respectively), but higher in rabbits (81%) and lower in mice (45%).

The blood to plasma ratios for abrocitinib in mice, rats, monkeys and humans were approximately 1, showing no preference for any compartment. In rabbits, there was a preference for the plasma compartment (ratio 0.59). Regarding the metabolites M1, M2 and M4, there was no preference for any compartment.

The metabolism of abrocitinib was examined *in vitro* in rat, monkey and human liver microsomes. The primary metabolic pathways were oxidative. *In vitro* human CYP phenotyping studies showed that CYP2C19 is the primary clearance route, followed by contributions from CYP2C9, CYP3A4 and CYP2B6.

The excretion of abrocitinib was investigated in bile and urine after single i.v. administration in rats, and in urine after repeated oral administration in rasH2-Tg mice. In rats, approximately 7% and 0.1% of the drug was eliminated unchanged in urine and bile, respectively. In mice, M4 was the major metabolite detected in urine.

In humans, following oral administration of 200 mg of ^{14}C-abrocitinib, approximately 85% radioactivity was recovered in urine and 10% in faeces. M1, M2 and M4 were predominant in pooled urine. All metabolites in faeces were less than 2% each.

The passage into milk was investigated in lactating rats after single oral administration of abrocitinib at 10 mg/kg. Concentrations of abrocitinib in milk were higher compared to plasma and measurable for up to 24 hours, while plasma concentrations were measurable for up to 8 hours. The recommendation for breastfeeding in the information for healthcare professionals is adequate.

5.3 Toxicology

The toxicological evaluation of abrocitinib was conducted in rats, rabbits and cynomolgus monkeys. The oral route of administration as well as the duration of the studies in rodents and non-rodents support the clinical use. The toxicity profile of abrocitinib was evaluated in toxicity studies with daily dosing for up to 6 months in rats (30, 45 or 70 mg/kg/day) and 9 months in monkeys (15, 35 or 75 mg/kg/day).

Toxicological findings occurred in rats and monkeys. The main target organs for toxicity were the haematopoietic and immune systems, bones and kidneys. The findings in the hematopoietic and immune system were caused by the mode of action of abrocitinib and occurred in rats and monkeys at 1- and 10-fold respectively of the unbound AUC_{24} at the maximum recommended human dose (MRHD).

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Significant immune suppression observed across the species was characterised by lymphocytopenia associated with the decrease in T-cells, T-cell subsets (helper and cytotoxic), plasma cells, B cells, and NK cells. Decreased lymphoid cellularity was observed in the spleen, thymus, lymph nodes, bone marrow and gut-associated lymphoid tissue. Polyoma virus infections in the prostate in rats and cytomegalovirus infections in various organs in monkeys were possibly related to this immunosuppression. Lymphocytopenia as well as increased incidence of Infections were observed in clinical studies.

In a dedicated *in vitro* immunotoxicity study, abrocitinib had no unanticipated effects on parameters of human cellular immune function or human cell-mediated host resistance.

Decreases in red blood cells and haemoglobin and decreases in platelets were observed in rats.

Abrocitinib-related bone dystrophy was observed only in repeat-dose studies in rats with a short duration ≤1 month at doses ≥75 mg/kg/day (mild) and 200 mg/kg/day (moderate), associated with exposures >24-fold the unbound human AUC_{24}. The administration of abrocitinib is not expected to pose a risk of effects on bone in adults at clinically relevant therapeutic doses based on the absence of effects on bone findings in the 6-month toxicity study in rats and in any of the cynomolgus monkey toxicity studies up to 9 months at exposures 26-fold the unbound human AUC_{24} at the MRHD.

Male and female rats showed crystalluria (calcium oxalate) at exposures 18-fold the clinical exposure. However, there was no histological correlate in the bladder. The obstructive crystal nephropathy in mice is a rodent-specific phenomenon related to highly concentrated urine and is not predicted to be a relevant human risk.

Safety margins are in general low. The toxicity concerns are adequately monitored clinically and adequate measures defined.

A fertility and early embryonic development study was conducted in male and female rats with oral administration of abrocitinib at doses up to 70 mg/kg/day. Effects on female fertility (lower fertility index, *corpora lutea*, implantation sites) and increased post-implantation loss were observed in rats at 70 mg/kg/day and ≥30 mg/kg/day, respectively, with exposures 29- and ≥11-fold the unbound human AUC_{24}. These effects were fully reversible following a 1-month recovery period.

Abrocitinib did not cause malformations in either rats or rabbits. In the embryo-foetal development study in rats, the average number of late resorptions per litter was increased at 60 mg/kg/day at exposures 17-fold the unbound human AUC_{24} at the MRHD. Skeletal variations (short 13th ribs and cervical arches with reduced ventral processes, thickened ribs and unossified metatarsals) occurred at 60 mg/kg/day. No adverse events were observed in rabbits. The product is contraindicated during pregnancy, and contraception is recommended for women of child-bearing potential.

In a pre-/post-natal development study in rats administered abrocitinib orally at 10, 30 or 60 mg/kg/day from gestation day 6 to lactation day 20, dystocia was observed at ≥30 mg/kg/day, and total litter loss occurred at 60 mg/kg/day. These findings were observed at exposures >10-fold the unbound human AUC_{24} at the MRHD.

In the juvenile toxicity study in rats with abrocitinib administered orally for 53 days (from day 10 of age) at doses of 5, 25 or 75 mg/kg/day, bent bones, malrotated paws and/or small/soft/misshapen femoral head were observed with histopathological abnormal morphology of the femoral head at all doses. These macroscopic and microscopic findings were not reversible. The exposure at 5 mg/kg/day corresponds to about 0.9-fold exposure at a clinical dose of 200 mg in adolescent patients. The findings indicate that abrocitinib could cause malformations in bone and lower bone length and width from toddler age up to adolescent populations. The key safety findings in bones observed in the juvenile study are included in the RMP together with the relevance to human usage in the adolescent population, as well as in the information for healthcare professionals.

Abrocitinib was not genotoxic in an Ames assay at concentrations up to 5,000 µg/plate. In the *in vitro* micronucleus assay in TK6 cells, a statistically significant increase in the percentage of cells with micronuclei was observed at concentrations of 37.4 and 43.6 µg/mL without metabolic activation. Based on additional investigations, micronucleus formation was due to an aneugenic mechanism. No increases in micronuclei were observed in an *in vivo* micronucleus assay in rats after oral administration

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of up to 600 mg/kg at exposures 114- fold the unbound human AUC_{24}. The genotoxic risk is therefore considered low.

In carcinogenicity studies in rasH2-Tg mice at 10, 20 or 60 mg/kg/day (males) and 10, 25 or 75 mg/kg/day (females) for up to 26 weeks, there were no abrocitinib-related neoplastic findings at exposures within clinical exposure. In rats administered 3, 10 or 30 mg/kg/day for up to 104 weeks, females at ≥10 mg/kg/day had a higher but not statistically significant incidence of large thymus, which correlated microscopically with benign thymomas. Based on the absence of genotoxicity, pre-neoplastic or neoplastic findings in the repeated toxicity studies in rats, absence of dose dependency in the incidence of benign thymomas and the presence of this finding with other JAK inhibitors, thymomas would not be considered a significant risk to humans, although there is no safety margin. Other types of malignancies than thymomas were observed in clinical studies with abrocitinib.

Abrocitinib was not phototoxic *in vivo* in Long Evans rats.

Based on the ERA, abrocitinib does not represent a risk for the environment at the prescribed dose.

5.4 Nonclinical Conclusions

In conclusion, the pharmaco-toxicological profile of abrocitinib is considered to be sufficiently well characterised. The submitted nonclinical data support the approval of Cibinqo in the proposed indication. The relevant information has been included in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

Biopharmaceutical Development

Throughout the entire clinical programme, different formulations of abrocitinib including an oral suspension, an oral solution and film-coated tablets have been developed and used. The final drug product will be commercialised as 50 mg and 100 mg strength immediate release film-coated tablets.
Bioequivalence of single 200 mg doses of the Phase 3 tablet formulation and commercial tablet formulation was demonstrated under fasting conditions.
AUC_{inf} and C_{max} of abrocitinib were increased by 26% and 29%, respectively, and T_{max} was prolonged by 1 h when co-administered with a high-fat, high-calorie breakfast. The proposed dosing recommendation to take the tablet irrespective of food consumption is acceptable and was applied in the Phase 3 studies.

ADME

Absorption

The pharmacokinetic profiles of abrocitinib and its major metabolites M1, M2 and M4 in healthy subjects following single (3 mg to 800 mg) and multiple doses (30 mg and 400 mg) were evaluated in 15 Phase 1 studies. Sparse pharmacokinetic samples were collected in the Phase 2 and 3 studies and contributed exclusively to the population PK analyses.

After a single dose of 100 mg abrocitinib in healthy subjects, the peak plasma concentrations of 519.8 ng/mL were reached after 1 h. Mean abrocitinib AUC_{inf} was 1,549.0 ng*h/mL. Absolute bioavailability (F) was estimated at 60% based on the PO/IV ratio of dose-normalised plasma AUC. Taking into account the total ^{14}C urinary excretion following PO and IV administration of ^{14}C-abrocitinib, the fraction absorbed (F_a) of abrocitinib was estimated at 91%. This difference between F and F_a may indicate a considerable first-pass effect, which is consistent with the liver extraction ratio and the role of CYP metabolism. Whereas the intra-individual variability was low for AUC of abrocitinib, intra-subject variability for C_{max} was estimated at 32%.

Following multiple QD doses of abrocitinib in healthy subjects, steady-state plasma concentrations of abrocitinib were reached after approximately 3 to 4 days. In the context of a population PK analysis, it was shown that C_{max} and AUC were increased by 27% and 31%, respectively, in AD patients compared to healthy subjects, which was not considered clinically relevant. Based on the population analysis, the steady-state accumulation ratio of abrocitinib for the QD dosing regimen of 200 mg in AD patients was estimated at 1.3.

Dose proportionality of abrocitinib can be considered demonstrated for QD doses between 30 mg and 400 mg.

Distribution

Based on in vitro findings, the fractions unbound (fu) in plasma for abrocitinib, M1, M2 and M4 were 0.36, 0.63, 0.71 and 0.83, respectively. Blood/plasma ratios of 1.07, 1.13, 1.27 and 0.87, respectively, for abrocitinib, M1, M2 and M4 suggest approximately equal distribution between red blood cells and plasma.

The volume of distribution at steady state was calculated to be 100.2 L after IV dosing.

Metabolism and Elimination

In vitro human CYP phenotyping studies showed that abrocitinib was metabolised by CYP2C19, CYP2C9, CYP3A4 and CYP2B6. Abrocitinib was excreted via urine and faeces, accounting for 85.0% and 9.5% of the total radioactivity, respectively. The predominant circulating entity was abrocitinib (25.8%) followed by M4 (13.8%), M2 (12.4%) and M1 (11%). All other metabolites accounted for <10% of the total radioactivity in plasma. The major metabolites in urine were M1, M2, M4 and M6, accounting for 16.2%, 13.5%, 15.4% and 12.0% of the administered radioactive dose, respectively, whereas only small amounts of the parent drug were present in urine (0.6%). The metabolites have been shown to be OAT3 substrates, indicating active renal secretion. Major metabolites in faeces were M1 and M7,

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accounting for 1.7% and 1.5%, respectively, of the administered radioactive dose. The low amounts of parent drug in urine and faeces suggest that abrocitinib is primarily eliminated by metabolism.

Since the parent drug as well as the metabolites M1 and M2 were shown to be pharmacologically active, the active moiety was defined as the unbound sum of the exposures of abrocitinib, M1 and M2 adjusted for their relative potencies based on the *in vitro* $IC_{50,u}$ for IFN-α.

Based on the population PK analysis, the initial clearance of abrocitinib was estimated at 22 L/h. The mean terminal half-lives of abrocitinib, M1, M2 and M4 were 5.9 h, 4.2 h, 3.9 h and 5.0 h, respectively, following a single dose of 200 mg abrocitinib and 6.0 h, 6.3 h, 4.6 h and 5.8 h, respectively, at steady state after multiple QD doses of 200 mg abrocitinib.

Special Populations / Intrinsic Factors

The impact of liver function on the pharmacokinetics of abrocitinib and its major metabolites following a single dose of 200 mg abrocitinib was investigated in a dedicated study in subjects with normal hepatic function and mild to moderate hepatic impairment. Increasing hepatic impairment was associated with increased abrocitinib exposures in subjects with mild and moderate hepatic impairment: AUC_{inf} +33% and +54%, respectively; C_{max}, -6% and +6%, respectively. Based on small changes in $C_{max,u}$ and $AUC_{inf,u}$ of the active moiety (<15%), no dose adjustments are recommended for patients with mild or moderate hepatic impairment. No patients with severe hepatic impairment were included.

The impact of kidney function on the pharmacokinetics of abrocitinib and its major metabolites following a single dose of 200 mg abrocitinib was investigated in a dedicated study in subjects with normal renal function and moderate to severe renal impairment. Increasing renal impairment was associated with increased abrocitinib exposures in subjects with moderate and severe renal impairment: AUC_{inf} +83% and +21%, respectively; C_{max}, +38% and -1%, respectively. Whereas the impact on $C_{max,u}$ of the active moiety was less pronounced, $AUC_{inf,u}$ was increased by 110% and 191%,respectively, in patients with moderate and severe renal impairment. In consideration of these findings, a dose reduction by half is recommended for patients with moderate renal impairment, whereas administration of abrotcitinib is not recommended for patients with severe renal impairment. Based on extrapolation using linear regression and in view of 100 mg being approved as the maximum dose, no dose adjustment for patients with mild renal impairment is recommended. No patients with ESRD were included.

Using data from seven Phase 1, two Phase 2 and two Phase 3 studies, a population PK analysis was conducted to identify factors that account for variability of the abrocitinib PK. The PK of abrocitinib was well described by a 2-compartment model with parallel zero- and first-order absorption, time-dependent absolute bioavailability (F) and time- and dose-dependent clearance (CL). The final model included the following covariates: co-administration of rifampin, fluconazole and fluvoxamine on CL; formulation and co-administration of a high-fat meal on absorption; and formulation, co-administration of rifampin, fluconazole and fluvoxamine, 800 mg dose, repeated dosing, race, disease status, mild and moderate hepatic impairment and gender (female participants) on F. Furthermore, an updated population PK analysis for both the parent drug and metabolites to simulate the PK of the active moiety at steady state was conducted. Although there are limitations, no dose adjustments are recommended based on gender, age, body weight and race.

No relevant differences in abrocitinib exposure were observed between different CYP2C9 and CYP2C19 phenotypes.

Interactions

The *in vitro* DDI risk assessment was conducted for the relevant enzymes and transporters at adequate concentrations of abrocitinib and its metabolites M1, M2 and M4.

Abrocitinib did not reversibly inhibit any of the investigated CYPs; however, abrocitinib was shown to be a time-dependent inhibitor of CYP2C19 (IC_{50} = 42 µM), CYP2D6 (IC_{50} = 92 µM) and CYP3A4/5 (IC_{50} = 40 µM – 81 µM) in the presence of NADPH. Abrocitinib was shown to induce CYP3A4, CYP2B6, CYP2C8 and CYP2C19. M1, M2 and M4 did not reversibly inhibit any of the investigated CYPs; however, they were shown to be weak time-dependent inhibitors of CYP3A, CYP2C19 and CYP2D6 above concentrations of 16.9 µM, 9.49 µM and 30 µM, respectively. M1 and M2 were shown to induce CYP2B6 and CYP1A2, whereas M4 only induced CYP1A2.

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Abrocitinib, M1, M2 and M4 did not show any reversible inhibition of the major UGT isoforms. Furthermore, abrocitinib did not inhibit SULT1E1, SULT1A1 or SULT2A1.

Abrocitinib was shown to be a substrate of P-gp and BCRP but not of the hepatic uptake transporters OATP1B1 and OATP1B3. Renal transporters were not investigated, which is acceptable as very little parent drug is excreted in urine. Abrocitinib inhibited P-gp (IC_{50} = 100.3 µM), BCRP (IC_{50} = 9.8 µM), OAT3 (IC_{50} = 26 µM), OCT1 (IC_{50} = 44.2 µM), MATE1 (IC_{50} =5.5 µM) and MATE1K (IC_{50} = 10.7 µM). M1, M2 and M4 were shown to be substrates of OAT3 but not of OAT1, OCT2, MATE1 and MATE2K. M1, M2 and M4 inhibited BCRP (IC_{50} = 44.9 µM – 79 µM), MATE1 (IC_{50} = 45.9 µM – 111.3 µM), MATE2K (IC_{50} = 50.8 µM – 121.4 µM) and OAT3 (IC_{50} = 44.6 µM – 61.3 µM).

Based on these *in vitro* findings, eight clinical DDI studies were conducted to investigate abrocitinib as a potential perpetrator and victim drug. Co-administration with fluvoxamine, a strong CYP2C19 and moderate CYP3A inhibitor, and fluconazole, a strong CYP2C19 and moderate CYP3A/CPY2C9 inhibitor, caused a 1.75- and 3.83-fold increase of abrocitinib exposures, respectively. Based on 1.91- and 2.55-fold increases in the AUC_{inf} of the active moiety, a dose reduction by half is recommended in patients receiving dual strong inhibitors of CYP2C19 and moderate inhibitors of CYP2C9, or strong inhibitors of CYP2C19 alone. Co-administration with rifampin, a strong inducer of CYP3A and CYP2C19 and a moderate inducer of CYP1A2, CYP2B6, CYP2C8 and CYP2C9, led to a decrease of abrocitinib and active moiety exposures by 88% and 56%, respectively. Since this decrease may be associated with reduced efficacy, co-administration of CYP inducers is not recommended. When co-administered with probenecid, an inhibitor of OAT3, abrocitinib and active moiety AUC_{inf} increased 1.28- and 1.66-fold, respectively. No dose adjustments are required.

Co-administration with abrocitinib did not have an impact on the exposures of oral contraceptives (ethinyl estradiol and levonorgestrel), midazolam (substrate for CYP3A), rosuvastatin (substrate of BCRP and OAT3) and metformin (substrate for MATE1/2 K and OCT2). Co-administration with abrocitinib resulted in a 1.53- and 1.40-fold increase of dabigatran, a substrate for P-gp, C_{max} and AUC_{inf}. No dose adjustments are required. Caution should be exercised with concomitant use of Cibinqo and dabigatran or P-gp substrates with a narrow therapeutic index, such as digoxin.

Although abrocitinib was shown to be a substrate of the intestinal efflux transporters P-gp and BCRP, no clinical DDI studies with inhibitors of these transporters were conducted. This is acceptable considering the high oral absorption with an estimated Fa of 91%. The solubility of abrocitinib was shown to be pH-dependent; therefore, interactions with drugs that increase gastric pH may reduce the absorption of abrocitinib.

Mechanism of Action and Primary Pharmacology

Abrocitinib inhibits JAK1 by blocking the ATP binding site. A 28-fold selectivity over JAK2, >340-fold over JAK3 and 43-fold over TYK2 has been shown in *in vitro* studies. Inhibition of JAK1 leads to the modulation of cytokines involved in the pathophysiology of AD.
The two pharmacologically active metabolites M1 and M2 exhibit similar inhibitory effects as the parent drug abrocitinib.

Secondary Pharmacology (Safety)

A thorough QT/QTc study in healthy subjects suggests the absence of an unacceptable prolongation in cardiac repolarisation compared to placebo following the administration of a single supratherapeutic dose of 600 mg abrocitinib.

6.2 Dose Finding and Dose Recommendation

The submitted dose finding documentation is based predominantly on the dose-ranging study B7451006, as well as the three pivotal studies.

In the randomised double-blind study B7451006, the following oral treatments were compared in parallel as monotherapy over 12 weeks in around 50 patients (only emollients were permitted as topical treatments):

– Abrocitinib 10 mg 1x1/day

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- Abrocitinib 30 mg 1x1/day
- Abrocitinib 100 mg 1x1/day
- Abrocitinib 200 mg 1x1/day
- Placebo

The highest abrocitinib dose of 200 mg/day was chosen on the basis of non-clinical toxicity data.

The patients had moderate to severe atopic dermatitis that could not be adequately controlled with topical treatment.

The primary endpoint was the percentage of patients who showed an almost complete clinical response after 12 weeks of treatment (IGA 0 or 1 and ≥ 2 points improvement). Other IGA-related, as well as common EASI-, NRS- and SCORAD-related, variables were investigated as secondary endpoints.

Adverse events were more frequent numerically with abrocitinib than with placebo, and a relevant proportion involved respiratory infections. Regarding TEAEs leading to treatment discontinuation and SAEs, no consistent dose responses were observed. No fatalities or prohibitive safety problems were described.

Based on the outcome of the dose finding study, abrocitinib was investigated at the doses of 100 mg and 200 mg in the submitted pivotal studies, both as monotherapy and adjunctive treatment with topical corticosteroids. As the dose increased in these studies, an increasing difference compared to placebo was described for the investigated efficacy endpoints. The data also indicated a dose-dependent increase in herpes infections and other safety problems.

6.3 Efficacy

The submitted evidence of efficacy is based predominantly on three pivotal studies: MONO-1 (B7451012), MONO-2 (B7451013) and COMPARE (B7451029).

Pivotal studies:

Monotherapy in adults (studies MONO-1 B7451012 & MONO-2 B7451013)

In these two randomised, double-blind 2:2:1 parallel-group comparative studies with the same design and size, placebo treatment was compared with abrocitinib treatment at the doses of 100 mg and 200 mg once daily over 12 weeks.

The primary endpoints were the percentages of patients who showed a clear clinical improvement after 12 weeks of treatment (IGA≤1, EASI75) compared to placebo. There was a clear clinical improvement in IGA with abrocitinib of 23.7% vs placebo 7.9% (MONO-1) and 28.4% vs 9.1% respectively (MONO-2) and in EASI-75 with abrocitinib of 39.7% vs placebo 11.8% (MONO-1) and 44.5% vs 10.4% respectively (MONO-2).

For details please refer to the attached information for healthcare professionals.

Combination treatment with topical corticosteroids in adults (Study COMPARE B7451029)

In this randomised, double-blind 2:2.2:1 parallel-group comparative study, the following interventions over 12-16 weeks were compared in adult patients (≥ 18 years) whose condition could not be adequately controlled with topical treatment: abrocitinib, dupilumab and placebo.

The basic treatments were cutaneous preparations (moderately strong corticosteroids on active lesions, weak topical corticosteroids on active lesions on critical body sites; calcineurin inhibitors or PDE4 inhibitors were permitted).

Primary and secondary endpoints were similar to those in the monotherapy studies (IGA, EASI at 12 weeks).

Regarding the primary and secondary endpoints, a statistically significant and clinically relevant better outcome was reported for abrocitinib and for dupilumab compared to placebo. There was a clear clinical improvement for IGA with abrocitinib of 36.6% vs placebo 14% and for EASI-75 with abrocitinib of 58.7% vs placebo 27.1% after 12 weeks.
For details please refer to the attached information for healthcare professionals.

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Key supportive studies

Study B7451014 (REGIMEN)

In this maintenance withdrawal study, open-label treatment for 12 weeks with abrocitinib 200 mg monotherapy was followed by a double-blind comparison of responders who were randomised to receive either placebo, abrocitinib 100 mg or abrocitinib 200 mg monotherapy. In the absence of a response, or if a response was lost, abrocitinib 200 mg in combination with topical corticosteroids was subsequently used as rescue medication.

The primary endpoint was the occurrence of a flare, defined as a loss of response (loss of at least 50% of EASI response at Week 12 and an IGA score of ≥2.)

A statistically significant, dose-dependent reduction in flares was described for both doses of abrocitinib.

In patients with an absent response or loss of response, the rescue treatment subsequently produced an improvement in all pre-treated patients, but this was more pronounced in those who lost the response while taking placebo than in those who were taking abrocitinib.

Long-term extension follow-up study B7451015 (EXTEND)

Patients in the pivotal "parent studies" (B7451012/B7451013/B7451029) could transfer to the still ongoing long-term extension follow-up study B7451015. Patients who had been treated with abrocitinib 100 mg or 200 mg in the parent studies continued, and are continuing this treatment, while patients who had been previously treated with placebo or dupilumab were randomised 1:1 either to the abrocitinib 100 mg or the abrocitinib 200 mg arm. At randomisation, the 100 mg arm comprised a total of 595 patients and the 200 mg arm 521 patients. In addition to abrocitinib, the patients were, and are, allowed to be treated with topical corticosteroids.

Among patients who did not achieve IGA (0 or 1) response after 12 weeks of abrocitinib treatment and entered EXTEND, 14% and 22% of patients continuing abrocitinib 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 abrocitinib 200 mg once daily achieved IGA response by Week 16 and Week 24, respectively (NRI-analysis).

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 abrocitinib treatment for both doses of abrocitinib (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 (NRI-Analysis)).

Conclusion:

Based on the submitted documentation, Swissmedic considers that the evidence presented demonstrates clinical efficacy in adults with moderate to severe atopic dermatitis who failed to respond adequately to topical corticosteroids alone.

6.4 Safety

The number of exposed patients/patient years in the Full Cumulative Pool was 3128/2088.8. Analyses were performed in different pools.

The “Primary Safety Pool” included all AD patients exposed to the study medication in randomised placebo-controlled studies (study periods). Data from this pool showed a higher number of TEAEs with abrocitinib compared to placebo.

The "All Exposure Pool" included all AD patients who were exposed in studies to abrocitinib 100 mg or 200 mg. Overall higher incidence rates are reported for SAEs and TEAEs resulting in permanent discontinuation. Fairly common events were infections, nausea, headache, dizziness, gastrointestinal disorders and acne. Slight dose-dependency was described for the frequencies of herpes infections (but not infections overall or severe infections), gastrointestinal disorders and headache.

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Adverse event of special interest

Serious dose-dependent clinical long-term sequelae observed during the experience to date with other JAK inhibitors include, in addition to thromboembolic events and infections, cardiovascular events, malignancies, gastrointestinal perforations and increased mortality.

Other relevant safety aspects

QTc prolongation

The "thorough QT study" B7451027 described a dose-dependent QTc prolongation, although a clinically relevant prolongation was observed only with clearly supratherapeutic exposures. No conclusive increase in cardiac problems was described for the investigated study population. However, patients with a QTcF interval of over 450 ms or with risk factors for torsades de pointes were excluded from the treatment.

Vaccination

The submitted vaccination/immunogenicity sub-study does not describe any impairment of the immune response during treatment with abrocitinib. However, the sub-study shows methodological shortcomings: the case numbers are small, results are not reported as specified in the protocol and the results submitted for the abrocitinib arms relate only to selected patients (8/9 abrocitinib 100 mg and 6/4 abrocitinib 200 mg; by contrast 10/10 placebo).

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

The clinical pharmacology package was extensive and covered all the relevant aspects. Population pharmacokinetic analyses revealed that no dose adjustments are necessary based on body weight, age, gender and race. No dose adjustments are recommended for patients with mild renal impairment and patients with mild or moderate hepatic impairment. No unacceptable prolongation in cardiac repolarisation was observed in a thorough QT/QTc study.

A dose reduction by half is recommended for patients with moderate renal impairment, whereas administration of abrotcitinib is no recommended for patients with severe renal impairment. A significant *in vitro* DDI risk was identified for abrocitinib and its metabolites. Based on clinical DDI studies, a dose reduction by half is recommended in patients receiving dual strong inhibitors of CYP2C19 and moderate inhibitors of CYP2C9, or strong inhibitors of CYP2C19 alone. Co-administration of CYP inducers is not recommended.

The submitted clinical documentation demonstrates benefits in patients with atopic dermatitis treated with abrocitinib compared to placebo regarding important clinical efficacy endpoints.

Long-term data for the JAK inhibitor tofacitinib indicate an increase in the risk of cardiac problems and malignancies. In February and September 2021, the U.S. Food and Drug Administration (FDA) stated that a long-term post-marketing study with the JAK inhibitor tofacitinib found an increased risk of cardiac problems and malignancies compared to tumour necrosis factor (TNF) inhibitors, and warned that other JAK inhibitors may pose similar risks based on the current data situation. Swissmedic carefully monitors these risks in the class of JAK inhibitors.

Overall, a positive benefit/risk profile has been shown for the treatment of atopic dermatitis patients with abrocitinib when all relevant precautions are taken into account in the following indication:

"Cibinqo is indicated for the treatment of moderate to severe atopic dermatitis in adults when therapy with topical medicinal products does not provide adequate disease control or cannot be used."

The recommended dosage is 100 mg once daily. If there is no sufficient improvement after 12 weeks of treatment, the medicinal product should be discontinued.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Cibinqo was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the «Undesirable effects» section for advice on the reporting of adverse reactions.

Cibinqo

Composition

Active substances

Abrocitinibum.

Excipients

50 mg film-coated tablets:

Tablet core: Cellulosum microcristallinum, calcii hydrogenophosphas, carboxymethylamylum natricum A (corresp. 0.81 mg sodium per film-coated tablet), magnesii stearas.

Film-coat: Hypromellosum (E464), titanii dioxidum (E171), lactosum monohydricum (corresp. 1.365 mg lactosum), macrogolum 3350, triacetinum, ferrum oxydatum rubrum (E172).

100 mg film-coated tablets:

Tablet core: Cellulosum microcristallinum, calcii hydrogenophosphas, carboxymethylamylum natricum A (corresp. 1.63 mg sodium per film-coated tablet), magnesii stearas.

Film-coat: Hypromellosum (E464), titanii dioxidum (E171), lactosum monohydricum (corresp. 2.73 mg lactosum), macrogolum 3350, triacetinum, ferrum oxydatum rubrum (E172).

Pharmaceutical form and active substance quantity per unit

50 mg film-coated tablets: One film-coated tablet contains 50 mg abrocitinib. The film-coated tablets are pink, oval, 10.50 mm long and 4.75 mm wide, debossed with «PFE» on one side and «ABR 50» on the other.

100 mg film-coated tablets: One film-coated tablet contains 100 mg abrocitinib. The film-coated tablets are pink, round, 9.00 mm in diameter, debossed with «PFE» on one side and «ABR 100» on the other.

Indications/Uses

Cibinqo is indicated for the treatment of moderate-to-severe atopic dermatitis in adults when therapy with topical medications does not provide adequate disease control or cannot be used.

Dosage/Administration

Treatment should be initiated and supervised by a healthcare professional experienced in the diagnosis and treatment of conditions for which Cibinqo is indicated (see section «Indications/Uses»).

Usual dosage

The recommended dose of Cibinqo is 100 mg once daily.

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

If there is no sufficient improvement after 12 weeks of treatment, the medication should be discontinued.

Treatment initiation

Treatment with Cibinqo should not be initiated in patients with a platelet count <150 × 10^3/mm^3, an absolute lymphocyte count (ALC) <0.5 × 10^3/mm^3, an absolute neutrophil count (ANC) <1 × 10^3/mm^3 or who have a haemoglobin value < 8 g/dL (see section «Warnings and precautions»).

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, interruption of Cibinqo until the infection is controlled should be considered (see section «Warnings and precautions»). Interruption of dosing may be needed for management of laboratory abnormalities as described in Table 1 (see section «Warnings and precautions»).

Special dosage instructions

Drug-drug interactions

In patients receiving dual strong inhibitors of cytochrome P450 (CYP)2C19 and moderate inhibitors of CYP2C9, or strong inhibitors of CYP2C19 alone (e.g. fluvoxamine, fluconazole, fluoxetine and ticlopidine), the recommended dose of Cibinqo should be reduced by half to 50 mg once daily.

The use of Cibinqo is not recommended concomitantly with moderate or strong inducers of CYP2C19/CYP2C9 enzymes (e.g. rifampin, apalutamide, efavirenz, enzalutamide, phenytoin) (see section «Interactions»).

Patients with impaired hepatic function

No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment (see section «Pharmacokinetics»). Cibinqo must not be usedin patients with severe (Child Pugh C) hepatic impairment (see section «Contraindications»).

Patients with impaired renal function

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

In patients with moderate (eGFR 30 to < 60 mL/min) renal impairment, the recommended dose of Cibinqo should be reduced by half to 50 mg once daily (see section «Pharmacokinetics»). Cibingo is not recommended in patients with severe (eGFR < 30mL/min) renal impairment.

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

Elderly patients

The risks and benefits of the recommended dose for patients ≥ 65 years of age should be considered (see section «Warnings and precautions»). There are no conclusive data in patients 75 years of age and older.

Children and adolescents

The safety and efficacy of Cibinqo in paediatric patients under 18 years of age have not yet been established.

Mode of administration

Cibinqo is to be taken orally once daily with or without food at approximately the same time each day. In patients who experience nausea while taking Cibinqo, taking with food may improve nausea. Cibinqo tablets should be swallowed whole with water and should not be split, crushed, or chewed.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section «Composition - Excipients».
- Active serious systemic infections, including tuberculosis (TB) (see section «Warnings and precautions»).
- Severe hepatic impairment (see section «Dosage/Administration»).
- Pregnancy and lactation (see section «Pregnancy, lactation»).

Warnings and precautions

Serious infections

Serious infections have been reported in patients receiving Cibinqo. The most frequent serious infections in clinical studies were herpes simplex, herpes zoster, and pneumonia, (see section «Undesirable effects»*)*.

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

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

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

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Cibinqo. A patient who develops a new infection during treatment with Cibinqo should undergo prompt and complete diagnostic testing which is appropriate for immunocompromised patients and appropriate antimicrobial therapy should be initiated. Discontinuation of Cibinqo should also be considered until the infection has resolved.

Tuberculosis

Patients should be screened for TB before starting Cibinqo therapy. Yearly screening for patients in highly endemic areas for TB should be considered. Cibinqo must not be given to patients with active TB (see section «Contraindications»). For patients with a new diagnosis of latent TB or prior untreated latent TB, preventive therapy for latent TB should be started prior to initiation of Cibinqo.

Viral reactivation

Viral reactivation, including herpes virus reactivation (e.g., herpes zoster, herpes simplex), was reported in clinical studies (see section «Undesirable effects»). The rate of herpes zoster infections was higher in patients 65 years of age and older and patients with severe atopic dermatitis at baseline (see section «Undesirable effects»). 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 Cibinqo. Patients with evidence of active hepatitis B or hepatitis C (positive hepatitis C PCR) infection were excluded from clinical studies (see section «Pharmacokinetics»). Patients who were hepatitis B surface antigen negative, hepatitis B core antibody positive, and hepatitis B surface antibody positive had testing for hepatitis B virus (HBV) DNA. Patients who had HBV DNA above the lower limit of quantification (LLQ) were excluded. Patients who had HBV DNA negative or below LLQ could initiate treatment with Cibinqo; such patients had HBV DNA monitored. If HBV DNA is detected, a liver specialist should be consulted.

Vaccination

No data are available on the response to vaccination with live or inactivated vaccines in patients treated with Cibinqo. Based on current data, it is not possible to assess the extent to which Cibinqo inhibits the immune response to neo- and/or booster antigens. Use of live, attenuated vaccines during or immediately prior to Cibinqo therapy is not recommended. The time interval between live vaccination and treatment with Cibinqo must be in accordance with current vaccination guidelines for immunomodulatory agents. Prior to initiating Cibinqo, it is recommended that patients be brought up to date with all immunisations, including prophylactic herpes zoster vaccinations, in agreement with current immunisation guidelines.

Gastrointestinal Perforations

Gastrointestinal perforation have rarely been observed during treatment with JAK inhibitors, as Cibinqo.

Venous thrombotic events including pulmonary embolism

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

Malignancy (including non-melanoma skin cancers)

Immunomodulatory drugs could increase the risk of tumor diseases including lymphoma. More cancer cases were observed with a JAK inhibitor other than abrocitinib in the treatment of rheumatoid arthritis versus TNF inhibitors. Malignancies, including non-melanoma skin cancer (NMSC), were observed in clinical studies with Cibinqo.

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

Haematologic abnormalities

Confirmed ALC <0.5 × 10^3/mm^3 and platelet count <50 × 10^3/mm^3 were observed in less than 0.5% of patients in clinical studies. Treatment with Cibinqo should not be initiated in patients with a platelet count <150 × 10^3/mm^3, an ALC <0.5 × 10^3/mm^3, an ANC <1 × 10^3/mm^3 or who have a haemoglobin value <8 g/dL (see section «Dosage/Administration»). Platelet count and ALC should be monitored 4 weeks after initiation of therapy with Cibinqo and thereafter according to routine patient management (see Table 1).

Lipids

Dose-dependent increase in blood lipid parameters were reported in patients treated with abrocitinib compared to placebo (see section «Undesirable effects»). Lipid parameters should be assessed

approximately 4 weeks following initiation of Cibinqo therapy and thereafter according to their risk for cardiovascular disease. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined. More serious adverse cardiac events have been observed with a JAK inhibitor other than abrocitinib compared with TNF inhibitors in the treatment of rheumatoid arthritis. Patients should be monitored and managed according to clinical guidelines, due to the known cardiovascular risks associated especially with hyperlipidaemia.

Laboratory monitoring

Table 1. Laboratory monitoring guidance

Laboratory measure	*Monitoring guidance*	*Action*
Platelet counts	Before treatment initiation, 4 weeks after initiation and thereafter according to routine patient management	Treatment should be discontinued if platelet counts are $<50 \times 10^3/mm^3$.
Absolute Lymphocyte Count (ALC)	Before treatment initiation, 4 weeks after initiation and thereafter according to routine patient management	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.
Lipid parameters	Before treatment initiation, 4 weeks after initiation and thereafter according to clinical guidelines for hyperlipidaemia	Patients should be monitored according to clinical guidelines for hyperlipidaemia.

Elderly

A total of 145 patients 65 years of age and older were enrolled in Cibinqo studies. The safety profile observed in elderly patients was similar to that of the adult population with the following exceptions: a higher proportion of patients 65 years of age and older discontinued from clinical studies and were more likely to have serious adverse events compared to younger patients; patients 65 years and older were more likely to develop low platelet and ALC values; the incidence rate of herpes zoster in patients 65 years of age and older was higher than that of younger patients (see section «Undesirable effects»). There are no conclusive data in patients above 75 years of age.

Excipients

Lactose intolerance

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

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablets meaning they are virtually «sodium free».

Interactions

Effect of Cibinqo on other medicinal products

The effect of abrocitinib on the pharmacokinetics of coadministered drugs is presented in Table 2.

Table 2. Change in Pharmacokinetics of Coadministered Drugs in the Presence of Abrocitinib

Coadministered Drugs or In Vivo Markers of CYP Activity	*Dose Regimen of Abrocitinib*	*Ratio[a] (90% Confidence Interval)*		*Dosing Recommendation*
		C_{max}	AUC_{inf}	
Oral contraceptive: Ethinyl estradiol (EE) and levonorgestrel (LN)	200 mg once daily x 9 days	EE: 1.07 (0.99, 1.15) LN: 0.86 (0.75, 0.97)	EE: 1.19 (1.12, 1.26) LN[b]: 0.98 (0.87, 1.10)	No dose adjustment
Sensitive CYP3A Substrate: Midazolam	200 mg once daily x 7 days	0.93 (0.84, 1.04)	0.92 (0.86, 0.99)	No dose adjustment
Sensitive P-gp substrate: Dabigatran	200 mg single dose	1.40 (0.92, 2.13)	1.53 (1.09, 2.15)	Caution should be exercised with concomitant use of Cibinqo with dabigatran or P-gp substrates with a narrow therapeutic index, such as digoxin
Sensitive BCRP and OAT3 substrate: Rosuvastatin	200 mg once daily x 3 days	0.99 (0.86, 1.14)	1.02 (0.93, 1.12)	No dose adjustment
Sensitive MATE1/2K substrate: Metformin	200 mg once daily x 2 days	0.88 (0.81, 0.96)	0.93 (0.85, 1.03)	No dose adjustment

[a]Ratios for C_{max} and AUC_{inf} compare coadministration of abrocitinib with the drug versus administration of the drug alone.
[b]AUC_{last} of levonorgestrel was reported in lieu of AUC_{inf} because the terminal phase of levonorgestrel was not well characterized.

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

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

Effect of other medicinal products on Cibinqo

Abrocitinib is metabolised predominantly by CYP2C19 and CYP2C9 enzymes, and to a lesser extent by CYP3A4 and CYP2B6 enzymes, and its active metabolites are renally excreted and are substrates of the organic anion transporter 3 (OAT3). Therefore, exposures of abrocitinib and/or its active metabolites may be affected by medicinal products that strongly inhibit or induce CYP2C19 or CYP2C9 or inhibit the OAT3 transporter. The effect of coadministered drugs on the pharmacokinetics of abrocitinib is presented in Table 3. Dose adjustments, as appropriate, based on these results are outlined in section «Dosage/Administration».

Table 3. Change in Pharmacokinetics of the Abrocitinib Active Moiety in the Presence of Coadministered Drugs

Coadministered Drugs	*Regimen of Coadministered Drug*	*Dose of Abrocitinib*	*Ratio[a] (90% Confidence Interval)*		*Dosing Recommendation*
			C_{max}	AUC_{inf}	
Strong CYP2C19 and moderate CYP3A inhibitor: Fluvoxamine[b]	50 mg once daily x 9 days	100 mg	1.33 (1.00-1.78)	1.91 (1.74-2.10)	Reduce Cibinqo dose by half to 50 mg once daily
Strong CYP2C19, moderate CYP2C9 and CYP3A inhibitor: Fluconazole[b]	400 mg on Day 1 and 200 mg on Days 2-7	100 mg	1.23 (1.08-1.42)	2.55 (2.42-2.69)	Reduce Cibinqo dose by half to 50 mg once daily
Strong CYP Enzymes Inducers: Rifampin[b]	600 mg once daily x 8 days	200 mg	0.69 (0.50-0.94)	0.44 (0.41-0.47)	Concomitant use is not recommended

OAT3 inhibitor: Probenecid[c]	1000 mg twice daily x 3 days	200 mg	1.30 (1.04-1.63)	1.66 (1.52-1.80)	No dose adjustment

[a] Ratios for C_{max} and AUC_{inf} compare coadministration of the drug with abrocitinib versus administration of abrocitinib alone.

[b] see section «Dosage/Administration»

[c] Drug interaction with OAT3 inhibitor is not clinically significant.

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.

Other in vitro interactions

In vitro, abrocitinib or its metabolites were not significant inhibitors or inducers of CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) or of uridine diphosphate glucuronyltransferases (UGTs) (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7). Abrocitinib or its metabolites at clinically meaningful concentrations are not inhibitors of organic anion transporter (OAT)3, organic cation transporter (OCT)1, multidrug and toxin compound extrusion protein (MATE)1/2K and breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1/1B3, bile salt export pump (BSEP), OAT1 or OCT2.

Pregnancy, lactation

Pregnancy

There are no or limited amount of data on the use of Cibinqo in pregnant women. Studies in animals have shown reproductive toxicity (see section «Preclinical data»). Cibinqo is contraindicated during pregnancy (see section «Contraindications»).

Women of childbearing potential

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

Lactation

There are no data on the presence of Cibinqo in human milk, the effects on the breast fed infant, or the effects on milk production. Cibinqo was secreted in milk of lactating rats. A risk to

newborns/infants cannot be excluded and Cibinqo is contraindicated during breast feeding (see section «Contraindications»).

Fertility

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

Effects on ability to drive and use machines

No studies have been conducted on the effect of Cibinqo on driving ability or ability to operate machinery. Patients should be informed that dizziness has been reported during treatment with Cibinqo (see «Adverse Effects »).

Undesirable effects

The most commonly reported adverse reactions occurring in ≥2% of patients treated with Cibinqo 200 mg in placebo-controlled studies are nausea (15.1%), headache (7.9%), acne (4.8%), herpes simplex (4.2%), blood creatine phosphokinase increased (3.8%), dizziness (3.4%) and upper abdominal pain (2.2%). The most frequent serious adverse reactions are infections (0.3%) (see section «Warnings and precautions»).

A total of 3’128 patients were treated with Cibinqo in clinical studies in atopic dermatitis representing 2’089 patient-years of exposure. There were 994 patients with at least 48 weeks of exposure. Five placebo controlled studies were integrated (703 patients on 100 mg once daily, 684 patients on 200 mg once daily and 438 patients on placebo) to evaluate the safety of Cibinqo in comparison to placebo for up to 16 weeks.

Listed in Table 4 are adverse reactions observed in atopic dermatitis clinical studies presented by system organ class and frequency, using the following categories: «very common» (≥1/10); «common» (≥1/100, <1/10); «uncommon» (≥1/1’000, <1/100); «rare» (≥1/10’000, <1/1’000); «very rare» (<1/10’000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4. Adverse reactions

System organ class	*Very common*	*Common*	*Uncommon*
Infections and infestations		Herpes simplex[a] Herpes zoster[b]	Pneumonia
Blood and lymphatic system disorders			Thrombocytopenia Lymphopenia
Metabolism and nutrition disorders			Hyperlipidaemia[c]
Nervous system disorders		Headache Dizziness	
Vascular disorders			Venous thrombotic events including pulmonary embolism[d]
Gastrointestinal disorders	Nausea (15.1%)	Vomiting Abdominal pain upper	
Skin and subcutaneous tissue disorders		Acne	
Investigations		Creatine phosphokinase increased > 5 × ULN[e]	

a. Herpes simplex includes oral herpes, ophthalmic herpes simplex, genital herpes, and herpes dermatitis.
b. Herpes zoster includes ophthalmic herpes zoster.
c. Hyperlipidaemia includes dyslipidaemia and hypercholesterolaemia.
d. Venous thromboic events include deep vein thrombosis.
e. Includes changes detected during laboratory monitoring (see text below).

Description of selected undesirable effects

Please note, that the 200 mg dose is not approved in Switzerland.

Infections

In placebo controlled studies, for up to 16 weeks, infections have been reported in 27.4% of patients treated with placebo and in 34.9% and 34.8% of patients treated with Cibinqo 100 mg. Most infections were mild or moderate. The percentage of patients reporting infection-related adverse drug reactions compared to placebo were: herpes simplex (2.8% vs 1.4%), herpes zoster (0.6% vs 0%), pneumonia (0.1% vs 0%). Herpes simplex was more frequent in patients with a history of herpes simplex or eczema herpeticum. Most of the herpes zoster events involved a single dermatome and were non-serious. All the opportunistic infections were cases of multidermatomal cutaneous herpes zoster (0.6%), most of which were non-serious. The incidence rate of herpes zoster in patients 65 years of age and older (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). The incidence rate of herpes zoster in patients with severe atopic dermatitis at baseline (4.93 per 100 patient-years) was higher than that of patients with moderate atopic dermatitis at baseline (2.49 per 100 patient-years) (see section «Warnings and precautions»).

In placebo controlled studies, for up to 16 weeks, the rate of serious infections was 1.81 per 100 patient-years in patients treated with placebo, 3.32 per 100 patient-years in patients treated with Cibinqo 100 mg.Among all patients treated with Cibinqo, including the long-term extension study, the rate of serious infections was 2.65 per 100 patient-years treated with Cibinqo 100 mg. The most commonly reported serious infections were herpes simplex, herpes zoster, and pneumonia (see section «Warnings and precautions»).

Venous thrombotic events including pulmonary embolism

Events were observed in the clinical trial program only during treatment with 200 mg, which is not approved in Switzerland (see section «Warnings and precautions»).

Thrombocytopenia

In placebo controlled studies, for up to 16 weeks, treatment was associated with a dose-related decrease in platelet count. Maximum effects on platelets were observed within 4 weeks, after which the platelet count returned towards baseline despite continued therapy. Confirmed platelet counts of $<50 \times 10^3/mm^3$ were reported in 0.1% of patients exposed to 200 mg., and in 0 patients treated with 100 mg or placebo. Among all patients exposed to Cibinqo, including the long-term extension study, confirmed platelet counts of $<50 \times 10^3/mm^3$ were reported in0.1% of patients treated with 200 mg, occurring at Week 4. A higher proportion of patients 65 years of age and older developed a platelet count nadir $< 75 \times 10^3/mm^3$ (see section «Warnings and precautions»).

Lymphopenia

In placebo controlled studies, for up to 16 weeks, confirmed ALC $<0.5 \times 10^3/mm^3$ occurred in 0.3% of patients treated with Cibinqo 200 mg and 0 % of patients treated with Cibinqo 100 mg or placebo. Both cases occurred in the first 4 weeks of exposure. Among all patients exposed to Cibinqo, including the long-term extension, confirmed ALC $<0.5 \times 10^3/mm^3$ were reported in 0.3% of patients treated with 200 mg and 0.1% of patients treated with 100 mg, all of whom were 65 years of age and older (see section «Warnings and precautions»).

Lipid elevations

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

to 100 mg, 0.6% of patients exposed to 200 mg and 0% of patients exposed to placebo (see section «Warnings and precautions»).

Creatine phosphokinase elevations (CPK)

In placebo controlled studies, for up to 16 weeks, significant increases in CPK values (> 5 × ULN) occurred in 1.8% of patients treated with placebo, 1.8% of patients treated with 100 mg . Most elevations were transient, and none led to discontinuation. In the clinical studies, there were no reported events of rhabdomyolysis.

Nausea

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

Children and adolescents (use in this age group is not approved in Switzerland)

A total of 635 adolescents (12 to less than 18 years of age) were enrolled in Cibinqo atopic dermatitis studies. The safety profile observed in adolescents in atopic dermatitis clinical studies was similar to that of the adult population (see section «Dosage/Administration»).

Psychiatric disorders

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

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Cibinqo was administered in clinical studies up to a single oral dose of 800 mg and 400 mg daily for 28 days. Adverse reactions were comparable to those seen at lower doses and no specific toxicities were identified. In case of an overdose, it is recommended that the patient be monitored for signs and

symptoms of adverse reactions (see section «Undesirable effects»). Treatment should be symptomatic and supportive.

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

Properties/Effects

ATC code

D11AH08

Mechanism of action

Cibinqo is a Janus kinase (JAK)1 inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of haematopoiesis and immune cell function. Within signalling pathways, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Cibinqo modulates the signalling pathway at the point of JAK1, preventing the phosphorylation and activation of STATs.
Cibinqo reversibly and selectively inhibits JAK1 by blocking the adenosine triphosphate (ATP) binding site. In a cell-free isolated enzyme assay, Cibinqo 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), Cibinqo preferentially inhibits cytokine-induced STAT phosphorylation mediated by receptors utilising JAK1 relative to receptors utilising JAK2 only or JAK2/TYK2 pairs. The relevance of selective enzymatic inhibition of specific JAK enzymes to clinical effect is not currently known. Both the parent compound and the active metabolites inhibit cytokine signalling with similar levels of selectivity.

Pharmacodynamics

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

Cardiac electrophysiology

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

Clinical efficacy

The efficacy and safety of Cibinqo as monotherapy and in combination with background medicated topical therapies over 12-16 weeks were evaluated in 1’616 patients in 3 pivotal Phase 3 randomised, double-blind, placebo-controlled studies (MONO-1, MONO-2, and COMPARE). In addition, the efficacy and safety of Cibinqo in monotherapy over 52 weeks (with the option of rescue treatment in flaring subjects) was evaluated in 1’233 subjects in a Phase 3 induction, randomised withdrawal, double-blind, placebo-controlled study (REGIMEN). The patients in these 4 studies had moderate-to-severe atopic dermatitis as defined by Investigator’s Global Assessment (IGA) score ≥3, Eczema Area and Severity Index (EASI) score ≥16, BSA involvement ≥10%, and Peak Pruritus Numerical Rating Scale (PP-NRS) ≥ 4 at baseline visit to randomisation. Patients who had a prior inadequate response or for whom topical treatments were medically unadvisable, or who had received systemic therapies were eligible for inclusion. All patients who completed the parent studies were eligible to enrol into the long-term extension study EXTEND.

Baseline characteristics
In the placebo-controlled studies (MONO-1, MONO-2, COMPARE) and the open label induction, randomised withdrawal study (REGIMEN) across all treatment groups 41.4% to 51.1% were female, 59.3% to 77.8% were Caucasian, 15.0% to 33.0% were Asian and 4.1% to 8.3% were Black, and the mean age was 32.1 to 37.7 years. In these studies, 32.2% to 40.8% had a baseline IGA of 4 (severe atopic dermatitis), and 41.4% to 59.5% of patients had received prior systemic treatment for atopic dermatitis. The baseline mean EASI score ranged from 28.5 to 30.9, the baseline PP-NRS ranged from 7.0 to 7.3 and the baseline Dermatology Life Quality Index (DLQI) ranged from 14.4 to 16.0.

Clinical response

12-week monotherapy (MONO-1, MONO-2) and 16-week TCS combination (COMPARE) studies
A significantly larger proportion of patients achieved both primary endpoints IGA 0 or 1 and/or EASI-75 with 100 mg once daily Cibinqo compared with placebo at Week 12 or Week 16 (see Table 5).

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

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

Table 5. Efficacy results of Cibinqo in monotherapy at Week 12

	MONO-1[c]		*MONO-2*[c]	
	Week 12		*Week 12*	
	CBQ monotherapy		*CBQ monotherapy*	
	100 mg QD N=156	*PBO N=77*	*100 mg QD N=158*	*PBO N=78*
	% Responders (95% CI)			
IGA 0 or 1[a]	23.7[d] (17.0, 30.4)	7.9 (1.8, 14.0)	28.4[d] (21.3, 35.5)	9.1 (2.7, 15.5)
EASI-75[b]	39.7[d] (32.1, 47.4)	11.8 (4.6, 19.1)	44.5[d] (36.7, 52.3)	10.4 (3.6, 17.2)
PSAAD[e]	-2.2[d] (-2.6, -1.9)	-1.1 (-1.7, -0.6)	-2.4[d] (-2.8, -2.1)	-0.8 (-1.3, -0.3)

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

a. IGA responders were patients with IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥ 2 points.
b. EASI-75 responders were patients with ≥ 75% improvement, in EASI from baseline.
c. Cibinqo in monotherapy.
d. Statistically significant with adjustment for multiplicity vs placebo.
e. Results shown are least squares mean change from baseline

Table 6. Efficacy results of Cibinqo in combination with topical therapy at Week 12 and Week 16

	COMPARE[c]					
	Week 12			*Week 16*		
	CBQ + topicals 100 mg N=238	*PBO + topicals N=131*	*DUP + topicals N=243*	*CBQ + topicals 100 mg N=238*	*PBO + topicals N=131*	*DUP + topicals N=243*
	% Responders (95% CI)					
IGA 0 or 1[a]	36.6[d] (30.4, 42.8)	14.0 (8.0, 19.9)	36.5 (30.4, 42.6)	34.8[d] (28.6, 40.9)	12.9 (7.0, 18.8)	38.8 (32.5, 45.1)
EASI-75[b]	58.7[d] (52.4, 65.0)	27.1 (19.5, 34.8)	58.1 (51.9, 64.3)	60.3[d] (53.9, 66.6)	30.6 (22.5, 38.8)	65.5 (59.4, 71.6)

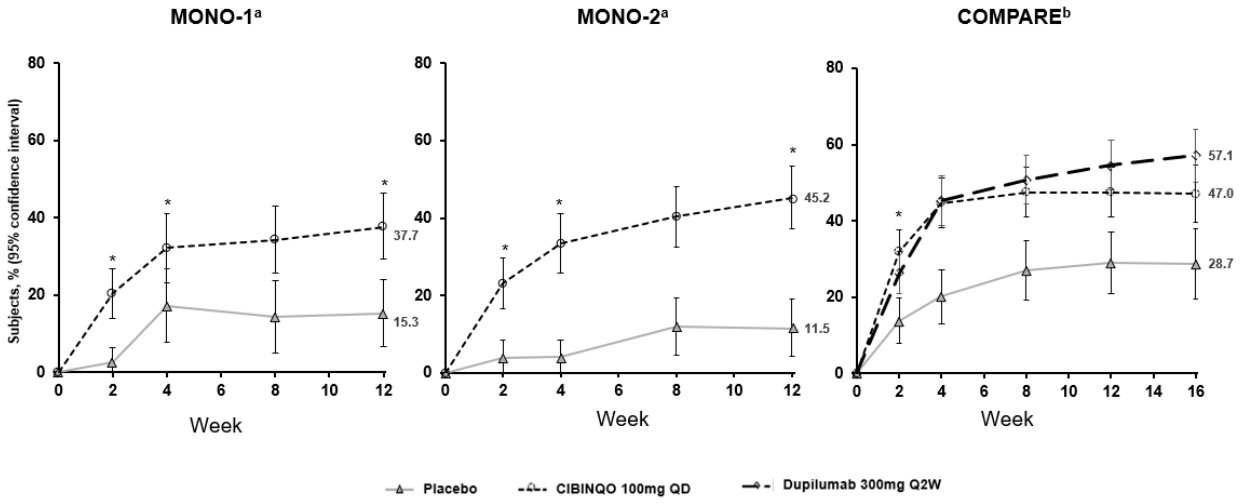
Abbreviations: CBQ=Cibinqo; CI=confidence interval; DUP=Dupilumab; EASI=Eczema Area and Severity Index; IGA=Investigator Global Assessment; N=number of patients randomised; PBO=placebo; PP-NRS=Peak Pruritus Numerical Rating Scale; PSAAD=Pruritus and Symptoms Assessment for Atopic Dermatitis.

a. IGA responders were patients with IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥ 2 points.
b. EASI-75 responders were patients with ≥ 75% improvement, in EASI from baseline.
c. Cibinqo in combination with topical therapy.
d. Statistically significant with adjustment for multiplicity vs placebo.

.

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

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



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

a. Cibinqo used in monotherapy.
b. Cibinqo used in combination with medicated topical therapy.
* Statistically significant with adjustment for multiplicity vs placebo.

Long-term efficacy

Eligible patients who completed the full treatment period of a qualifying parent study (e.g. MONO-1, MONO 2, COMPARE) were considered for enrolment with or without background medicated topical

therapy in the long-term extension study EXTEND. Patients continued the same dose as they were randomized to in the parent study and the blind was maintained. The majority of patients on Cibinqo 100 mg once daily maintained their response at Week 48 of cumulative treatment [60% for IGA (0 or 1) response, 79% EASI-75, and 62% for PP-NRS4].

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

Pharmacokinetics

Absorption

Abrocitinib is well-absorbed with over 91% extent of oral absorption and absolute oral bioavailability of approximately 60%. The oral absorption of abrocitinib is rapid and peak plasma concentrations are reached within 1 hour. Both C_{max} and AUC of abrocitinib increased dose proportionally from 30 to 400 mg. After single 100 mg doses in healthy adult subjects, the mean (%CV) of abrocitinib AUC and C_{max} were 1549 (75) and 519.8 (79), respectively. Co-administration of Cibinqo with a high-fat meal had no clinically relevant effect on abrocitinib exposures (AUC and C_{max} increased by approximately 26% and 29%, respectively, and T_{max} was prolonged by 2 hours). In clinical studies, Cibinqo was administered without regard to food (see section «Dosage/Administration»).

Distribution

After intravenous administration, the volume of distribution of Cibinqo 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 *in vitro* metabolism of abrocitinib is mediated by multiple CYP enzymes, CYP2C19 (~53%), CYP2C9 (~30%), CYP3A4 (~11%) and CYP2B6 (~6%). In a human radiolabeled study, abrocitinib was the most prevalent circulating species, with 3 polar mono-hydroxylated metabolites identified as M1 (3-hydroxypropyl), M2 (2-hydroxypropyl), and M4 (pyrrolidinone pyrimidine). At steady state, M2 (11%) and M4 (24%) are major metabolites and M1 (9.6%) is a minor metabolite. Of the 3 metabolites in circulation, M1 and M2 have similar JAK inhibitory profiles as abrocitinib, while M4 was

pharmacologically inactive. The pharmacologic activity of Cibinqo 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

The total body clearance of abrocitinib is 22 L/hr. The elimination half-life of abrocitinib is about 6 hours. Steady state plasma concentrations of abrocitinib are achieved within 48 hours after once daily administration. After a 200 mg oral administration of [^{14}C]-abrocitinib in humans, total recovery of radioactivity was approximately 95%, with approximately 85% recovered in urine and 10% in feces. Cibinqo is eliminated primarily by metabolic clearance mechanisms, with less than 1% of the dose excreted in urine as unchanged drug. The urinary excretion of the metabolites of abrocitinib is 16%, 14% and 15% of the administered abrocitinib dose for M1, M2 and M4, respectively, and the metabolites are substrates of OAT3 transporter.

Kinetics in specific patient groups

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 «Dosage/Administration»). In clinical studies, Cibinqo was not evaluated in patients with severe (Child Pugh C) hepatic impairment (see section «Contraindications»), or in patients screened positive for active hepatitis B or hepatitis C (see section «Warnings and precautions»).

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 «Dosage/Administration»). Pharmacokinetics of abrocitinib have not been determined in patients with mild renal impairment, however, based on the results observed in other groups, an increase of up to 70% in active moiety exposure is expected in patients with mild renal impairment (eGFR 60 to< 90 mL/min). The increase of up to 70% is not clinically meaningful as the efficacy and safety of abrocitinib in atopic dermatitis patients with mild renal impairment (n=756) was comparable to the overall population in Phase 2 and 3 clinical studies. The eGFR in individual patients was estimated using Modification of Diet in Renal Disease (MDRD) formula.

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

Children and adolescents (use in this age group is not approved in Switzerland)

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

Body weight, gender, genotype, race, and age

Body weight (34-204 kg), gender, CYP2C19/2C9 genotype, race (white, asian, black, other), and age (12-84 years) did not have a clinically meaningful effect on Cibinqo exposure (see section «Dosage/Administration»).

Preclinical data

General toxicity

In toxicity studies of up to 1 month of Cibinqo dosing in rats initiated at 6-8 weeks and 9-weeks of age, a bone dystrophy findingwas noted, at exposure of greater than or equal to 46 times the human AUC at the maximum recommended human dose (MRHD) of 100 mg. No bone findings were observed in rats at any dose in the 6-month toxicity study (up to 50 times the human AUC at the MRHD of 100 mg) or in any of the toxicity studies in cynomolgus monkeys (up to 60 times the human AUC at the MRHD of 100 mg).

Mutagenicity

Cibinqo is not mutagenic in the bacterial mutagenicity assay (Ames assay). Although Cibinqo is aneugenic in the *in vitro* TK6 micronucleus assay, Cibinqo is not aneugenic or clastogenic at clinically relevant exposures 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 Cibinqo for 26 weeks at exposures equal to 1.2 and 0.4 times the human AUC at the MRHD of 100 mg in female and male mice, respectively. In the 104-week oral carcinogenicity study, Cibinqo resulted in statistically higher

incidence of benign thymomas in female rats at exposures greater than or equal to 5.4 times the human AUC at the MRHD of 100 mg. No evidence of Cibinqo-related tumorigenicity was observed following oral Cibinqo administration in female rats at exposures equal to 1.2 times the human AUC at the MRHD of 100 mg or in male rats at exposures equal to 26 times the human AUC at the MRHD of 100 mg.

Reproductive toxicity

Cibinqo had no effects on male fertility or spermatogenesis at doses up to 70 mg/kg/day at exposures equal to 50 times the human AUC at the MRHD of 100 mg. Cibinqo resulted in effects on female fertility (lower fertility index, *corpora lutea*, and implantation sites) at exposures equal to 56 times the human AUC at the MRHD of 100 mg and higher postimplantation loss in rats at exposures greater than or equal to 20 times the human AUC at the MRHD of 100 mg. The effects on female fertility in rats reversed 1 month after cessation of Cibinqo administration. No effects on female fertility were noted at exposures equal to 3.8 times the human AUC at the MRHD of 100 mg.

No foetal malformations were observed in embryo-foetal development studies in rats or rabbits. In an embryo-foetal development study in pregnant rabbits, oral administration of Cibinqo during gestation days 7 to 19 had no effects on embryo-foetal survival or foetal morphological development at exposures equal to 15.2 times the human AUC at the MRHD of 100 mg. Cibinqo resulted in an increase incidences of unossified forelimb phalanges at exposures equal to 15.2 times the human AUC at the MRHD of 100 mg.

In an embryo-foetal development study in pregnant rats, oral administration of Cibinqo during gestation days 6 to 17 resulted in increased embryo-foetal lethality at exposures equal to 32 times the human AUC at the MRHD of 100 mg. No embryo-foetal lethality was observed in pregnant rats orally dosed with Cibinqo during organogenesis at exposures equal to 20 times the human AUC at the MRHD of 100 mg. Cibinqo resulted in increased incidences of skeletal variations of short 13th ribs at exposures greater than or equal to 20 times the human AUC at the MRHD of 100 mg and reduced ventral processes, thickened ribs, and unossified metatarsals were observed at exposures equal to 32 times the human AUC at the MRHD of 100 mg. No skeletal variations were noted in rats at exposures equal to 4.6 times the human AUC at the MRHD of 100 mg.

In a rat pre- and postnatal development study in pregnant rats, oral administration of Cibinqo during gestation day 6 through lactation day 21 resulted in dystocia with prolonged parturition and lower offspring body weights at exposures greater than or equal to 20 times the human AUC at the MRHD of 100 mg and lower postnatal survival at exposures equal to 32 times the human AUC at the MRHD

of 100 mg. No maternal or developmental toxicity was observed in either dams or offspring at exposures equal to 4.6 times the human AUC at the MRHD of 100 mg.

Juvenile animal toxicity

In the juvenile rat study, oral administration of Cibinqo to rats initiated at postnatal Day 10 resulted in bone findings (malrotated and/or impaired use of the forelimbs, hindlimbs, or paws, fractures and/or abnormalities of the femoral head, and bony dystrophy), at exposures ≥1.6 times the human AUC at the MRHD of 100 mg. Irreversible low femur length and width were observed at exposures 52 times the human AUC at the MRHD of 100 mg.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date («EXP») stated on the container.

Special precautions for storage

Do not store above 30 °C.
Store in the original packaging.
Keep out of the reach of children.

Authorisation number

68174 (Swissmedic).

Packs

50 mg film-coated tablets: Carton with HDPE bottles containing 14 or 30 film-coated tablets. [B]
50 mg film-coated tablets: Carton with blisters containing 14, 28, or 91 film-coated tablets (7 film-coated tablets per blister). [B]

100 mg film-coated tablets: Carton with HDPE bottles containing 14 or 30 film-coated tablets. [B]
100 mg film-coated tablets: Carton with blisters containing 14, 28, or 91 film-coated tablets (7 film-coated tablets per blister). [B]

Marketing authorisation holder

Pfizer AG, Zürich.

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March 2022