Summary Report of Benefit-Risk Assessment

CIBINQO FILM COATED TABLETS 50MG, 100MG, 200MG

NEW DRUG APPLICATION

Active Ingredient(s)	Abrocitinib
Product Registrant	Pfizer Private Limited
Product Registration Number	SIN16412P, SIN16413P, SIN16414P
Application Route	Full Evaluation
Date of Approval	5 January 2022

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A INTRODUCTION

Cibinqo is indicated for the treatment of moderate-to-severe atopic dermatitis (AD) in adults (age 18 years and above) who are candidates for systemic therapy and whose disease is not adequately controlled with topical medications or for whom topical treatments are otherwise medically inadvisable.

The active substance, abrocitinib, is a Janus kinase (JAK)1 inhibitor that selectively inhibits JAK1 by blocking the adenosine triphosphate (ATP) binding site, which in turn prevents the phosphorylation and activation of Signal Transducers and Activators of Transcription (STATs). The JAK-STAT signalling pathway is the common transduction pathway for Type 1 and Type 2 cytokine receptors in response to inflammatory and proliferative signals.

Cibinqo is available as a film-coated tablet containing 50mg, 100mg or 200mg of abrocitinib. Other ingredients in the tablet core are microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate and magnesium stearate. Ingredients in the film coating include hypromellose, titanium dioxide, lactose monohydrate, macrogol, triacetin and iron red oxide.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, abrocitinib, is manufactured at Pfizer Ireland Pharmaceuticals, County Cork, Ireland. The drug product, Cibinqo Film-Coated Tablet 50mg, 100mg and 200mg, is manufactured at Pfizer Manufacturing Deutschland GmbH, Freiburg, Germany.

Drug substance:
Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented was adequate to support storage at 30°C/75%RH with a re-test period of 24 months. The packaging is double antistatic LDPE bags in a HDPE drum.

Drug product:
The tablet is manufactured by continuous manufacturing for feeding, mixing and direct compression of the tablets, followed by a batch process for film-coating.

The manufacturing site is compliant with Good Manufacturing Practice. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 30 months for 200mg and 100mg tablets and 24 months for 50mg tablet when stored below 30 ºC. The container closure system is a polyvinylchloride (PVC)/polyvinylidene chloride (PVDC) blister with an aluminium foil lidding.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of abrocitinib was based on 3 pivotal studies (B7451012, B7451013, B7451029) and a supportive safety study (B7451015).

Studies B7451012, B7451013 (Monotherapy Studies)

B7451012 and B7451013 were Phase 3, randomized, double-blind, placebo-controlled, parallel group, multi-centre studies of abrocitinib compared with placebo in patients with moderate-to-severe AD who had a documented history of inadequate response to topical medications or whom topical treatments are medically inadvisable. Patients were randomized in a 2:2:1 ratio to receive abrocitinib 100mg once daily (OD), abrocitinib 200mg OD or placebo once daily, respectively, for 12 weeks.

The primary efficacy endpoint was the co-primary endpoint of Investigator's Global Assessment (IGA) and Eczema Area and Severity Index (EASI), defined as the proportion of patients with an IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥ 2 points at Week 12 and the proportion of patients achieving the EASI-75 response (75% improvement from baseline) at Week 12. The key secondary endpoints included response based on ≥ 4 points improvement from baseline in the Peak Pruritus Numeric Rating Scale (PP-NRS4) at Weeks 2, 4, and 12, and the change from baseline in Pruritus and Symptoms Assessment for AD (PSAAD) at Week 12.

A total of 778 patients were randomized in the studies: 309 patients in the abrocitinib 200mg arm, 314 patients in the abrocitinib 100mg arm and 155 patients in the placebo arm. The median age was 29.0 years and 31.0 years in B7451012 and B7451013 respectively, and majority of the patients were White (72.1% and 59.3%). There were 47.8% and 57.8% of patients in B7451012 and B7451013, respectively, who were previously treated with topical agents only, and 48.3% and 41.4% of patients had received prior systemic agents.

Both studies demonstrated a dose-response and statistically significant differences between abrocitinib and placebo. In Study B7451012, the differences in the proportion of patients with IGA0/1 and reduction from baseline of ≥ 2 points at Week 12 were 15.8% with abrocitinib 100mg and 36.0% with abrocitinib 200mg compared to placebo, and the differences in the proportions of patients who achieved EASI-75 at Week 12 were 27.9% with abrocitinib 100mg and 51.0% with abrocitinib 200mg. Consistent results were seen in Study B7451013, with abrocitinib 100mg and 200mg demonstrated 19.3% and 28.7% improvements in the proportion of patients with IGA0/1 and reduction from baseline of ≥ 2 points at Week 12 compared to placebo. Similarly, the proportions of patients who achieved EASI-75 at Week 12 were significantly higher in the abrocitinib 100mg and 200mg arms, with differences of 33.9% and

50.5% respectively, compared to placebo. The key secondary endpoints showed that both treatment arms had statistically significantly greater proportions of PP-NRS4 responders compared with the placebo arm across all timepoints (Week 2, 4 and 12). Similar results were also demonstrated for the change from baseline in PSAAD at Week 12.

Summary of Key Efficacy Results (B7451012 and B7451013)

	B7451012			B7451013		
	Placebo N=77	**Abrocitinib 100mg OD N=156**	**Abrocitinib 200mg OD N=154**	**Placebo N=78**	**Abrocitinib 100mg OD N=158**	**Abrocitinib 200mg OD N=155**
Co-primary Endpoints						
IGA 0 or 1 and ≥2 points improvement at Week 12						
% responders	7.9	23.7	43.8	9.1	28.4	38.1
95% CI	1.8, 14.0	17.0, 30.4	35.9, 51.7	2.7, 15.5	21.3, 35.5	30.4, 45.7
Active – placebo						
Estimate (%)		15.8	36.0		19.3	28.7
95% CI		6.8, 24.8	26.2, 45.7		9.6, 29.0	18.6, 38.8
p-value		0.0037	<0.0001		0.0008	<0.0001
EASI-75 at Week 12						
% responders	11.8	39.7	62.7	10.4	44.5	61.0
95% CI	4.6, 19.1	32.1, 47.4	55.1, 70.4	3.6, 17.2	36.7, 52.3	53.3, 68.7
Active – placebo						
Estimate (%)		27.9	51.0		33.9	50.5
95% CI		17.4, 38.3	40.5, 61.5		23.3, 44.4	40.0, 60.9
p-value		<0.0001	<0.0001		<0.0001	<0.0001
Key Secondary Endpoints						
PP-NRS4 at Week 2						
% responders	2.7	20.4	45.6	3.9	23.1	35.3
95% CI	0.0, 6.4	13.9, 26.9	37.5, 53.6	0.0, 8.3	16.5, 29.7	27.7, 42.9
Active – placebo						
Estimate (%)		18.0	42.5		19.2	31.2
95% CI		10.2, 25.8	33.6, 51.4		11.0, 27.4	22.3, 40.2
p-value		0.0004	<0.0001		0.0002	<0.0001
PP-NRS4 at Week 4						
% responders	17.2	32.2	58.8	4.0	33.4	52.8
95% CI	7.7, 26.7	23.3, 41.1	49.5, 68.2	0.0, 8.4	25.8, 41.0	44.7, 60.8
Active – placebo						
Estimate (%)		15.0	41.1		29.5	48.8
95% CI		1.9, 28.0	27.8, 54.4		20.5, 38.4	39.5, 58.2
p-value		0.0251	<0.0001		<0.0001	<0.0001
PP-NRS4 at Week 12						
% responders	15.3	37.7	57.2	11.5	45.2	55.3
95% CI	6.6, 24.0	29.2, 46.3	48.8, 65.6	4.1, 19.0	37.1, 53.3	47.2, 63.5
Active – placebo						
Estimate (%)		22.5	41.7		33.7	43.9
95% CI		10.3, 34.8	29.6, 53.9		22.8, 44.7	32.9, 55.0
p-value		0.0003	<0.0001		<0.0001	<0.0001
Change in PSAAD at Week 12						
Least Square Mean Change	-1.1	-2.2	-3.2	-0.8	-2.4	-3.0
95% CI	-1.7, -0.6	-2.6, -1.9	-3.6, -2.8	-1.3, -0.3	-2.8, -2.1	-3.3, -2.7
Active – placebo						
Estimate (%)		-1.1	-2.1		-1.7	-2.2
95% CI		-1.7, -0.4	-2.7, -1.4		-2.3, -1.1	-2.8, -1.6
p-value		0.0010	<0.0001		<0.0001	<0.0001

N=number of patients randomized and treated

Study B7451029

B7451029 was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multi-centre study to assess the efficacy and safety of abrocitinib and dupilumab compared with placebo in moderate-to-severe AD adult patients on background topical therapy. Patients were randomized in a 2:2:2:1 ratio to receive abrocitinib 100mg and 200mg OD, dupilumab 300mg every two weeks (Q2W) and placebo, respectively, for 16 weeks. The primary efficacy endpoint was similar to studies B7451012 and B7451013, while the key secondary endpoints included the proportion of patients achieving PP-NRS4 at Week 2, proportion of patients achieving IGA0/1 and ≥ 2 points improvement from baseline at Week 16 and proportion of patients achieving EASI-75 at Week 16.

A total of 837 patients were randomized: 238 in abrocitinib 100mg OD arm, 226 patients in abrocitinib 200mg OD arm, 242 patients in dupilumab 300mg Q2W arm and 131 patients in placebo arm. The median age was 34.0 years and majority of the patients were White (72.4%). Approximately 56.5% of patients had received only topical agents (mostly topical corticosteroids) and 43.2% had received systemic agents (non-biologic or biologic, excluding dupilumab). No patients have used dupilumab prior to enrolment.

Similar to the results of studies B7451012 and B7451013, the clinical efficacy of abrocitinib in patients on background topical therapy was demonstrated in terms of the co-primary endpoints. The proportion of patients with IGA0/1 and reduction from baseline of ≥ 2 points at Week 12 was statistically and dose-dependently higher compared to placebo, with a difference of 23.1% and 34.8% for abrocitinib 100mg and 200mg respectively. Likewise, abrocitinib 100mg and 200mg demonstrated 31.9% and 43.2% improvements in the proportion of patients who achieved EASI-75 at Week 12. Efficacy results were maintained through Week 16. Although not statistically tested, the abrocitinib 200mg arm was numerically superior when compared against the active comparator, dupilumab, while the 100mg arm was generally comparable. Both doses of abrocitinib were also statistically superior to placebo for all the key secondary endpoints.

Summary of Key Efficacy Results (B7451029)

	B7451029			
	Placebo N=131	**Abrocitinib 100mg OD N=238**	**Abrocitinib 200mg OD N=226**	**Dupilumab 300mg Q2W N=242**
Co-primary Endpoints				
IGA 0 or 1 and ≥2 points improvement at Week 12				
% responders	14.0	36.6	48.4	36.5
95% CI	8.0, 19.9	30.4, 42.8	41.8, 55.0	30.4, 42.6
Active – placebo				
Estimate (%)		23.1	34.8	22.5
95% CI		14.7, 31.4	26.1, 43.5	14.2, 30.9
p-value		<0.0001	<0.0001	-
EASI-75 at Week 12				
% responders	27.1	58.7	70.3	58.1
95% CI	19.5, 34.8	52.4, 65.0	64.3, 76.4	51.9, 64.3
Active – placebo				
Estimate (%)		31.9	43.2	30.9
95% CI		22.2, 41.6	33.7, 52.7	21.2, 40.6
p-value		<0.0001	<0.0001	-
Key Secondary Endpoints				
PP-NRS4 at Week 2				
% responders	13.8	31.8	49.1	26.4

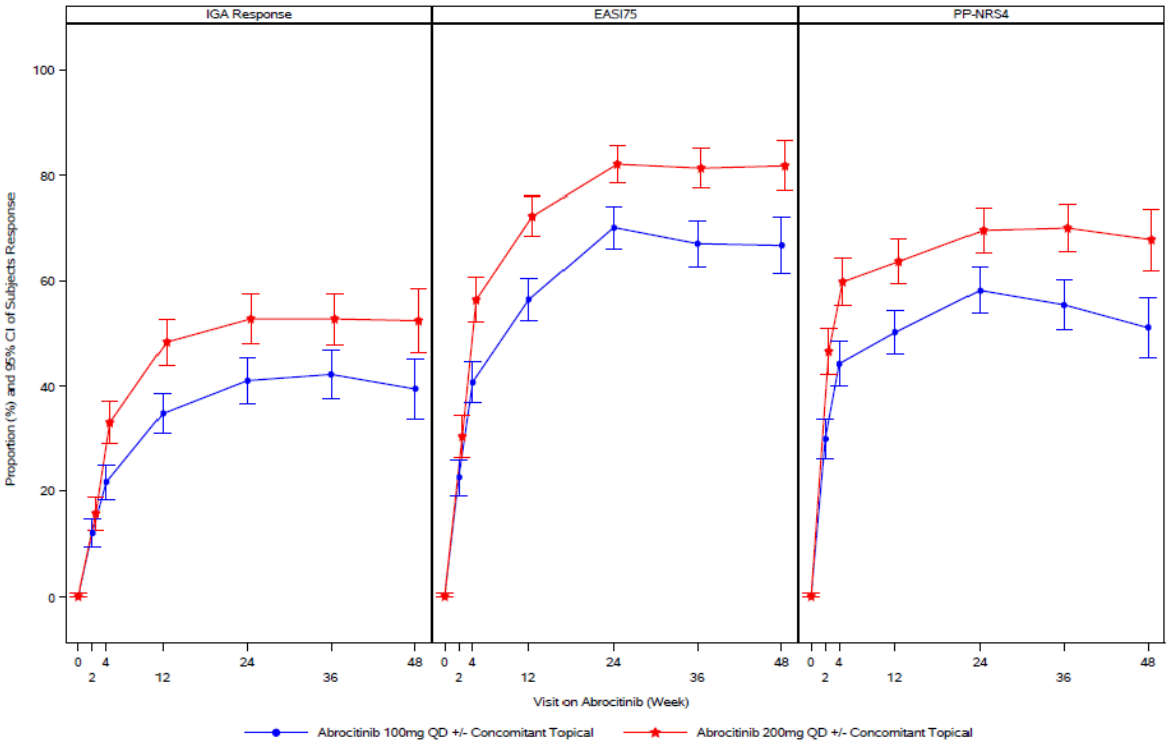
95% CI	7.9, 19.8	25.8, 37.7	42.6, 55.6	20.8, 31.9
Active – placebo				
Estimate (%)		17.9	34.9	12.5
95% CI		9.5, 26.3	26.0, 43.7	4.4, 20.7
p-value		0.0002	<0.0001	-
IGA 0 or 1 and ≥2 points improvement at Week 16				
% responders	12.9	34.8	47.5	38.8
95% CI	7.0, 18.8	28.6, 40.9	40.9, 54.1	32.5, 45.1
Active – placebo				
Estimate (%)		22.1	35.0	25.6
95% CI		13.7, 30.5	26.3, 43.7	17.1, 34.1
p-value		<0.0001	<0.0001	-
EASI-75 at Week 16				
% responders	30.6	60.3	71.0	65.5
95% CI	22.5, 38.8	53.9, 66.6	65.1, 77.0	59.4, 71.6
Active – placebo				
Estimate (%)		29.7	40.4	34.7
95% CI		19.5, 39.9	30.4, 50.4	24.6, 44.8
p-value		<0.0001	<0.0001	-

N=number of patients randomized and treated

Study B7451015

Study B7451015 was an on-going, long-term extension Phase 3 study, where eligible patients in the pivotal studies (B7451012, B7451013 and B7451029) were allowed to be enrolled. Eligible patients who were on abrocitinib 100mg or 200mg OD in the preceding studies continued the existing therapy. For patients who were treated with placebo or dupilumab, they were randomized in a 1:1 ratio to receive either abrocitinib 100mg or 200mg OD. The efficacy endpoints were similar to the pivotal studies (i.e., IGA response, EASI scores and PP-NRS4).

A total of 1,116 patients were randomized to both groups. The proportion of long-term therapy patients (on abrocitinib therapy and continued their existing treatment) who achieved an IGA score of 0/1 and at least 2 points improvement, EASI-75 and PP-NRS4 at Week 12 were maintain through Week 48 for both abrocitinib 100mg and 200mg arms.



Overall, the results of the studies were consistent in meeting the primary and secondary efficacy endpoints, and adequately supported the efficacy of abrocitinib for the treatment of moderate-to-severe AD in adults.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of abrocitinib was primarily supported by the Primary Pool and All-Exposure Pool. The Primary Pool included all patients given abrocitinib and compared against placebo with a study duration of 12-16 weeks, while the All-Exposure Pool was made up of patients who received at least one dose of abrocitinib in all Phase 2b and 3 studies in atopic dermatitis.

The Primary Pool included a total of 1,540 patients, with 608 exposed to abrocitinib 100mg, 590 exposed to 200mg, and 342 exposed to placebo. The median duration of exposure in abrocitinib treated subjects was 86.0 days. As of 22 April 2020, there were 2,856 patients included in the All-Exposure Pool, with 885 exposed to abrocitinib 100mg and 1,971 exposed to 200mg, representing 1614 patient-years of exposure. There were 606 patients exposed for at least 48 weeks and 198 for at least 72 weeks.

Overview of safety profile (Primary pool)

	Placebo (N=342) n (%)	**Abrocitinib 100mg OD (N=608) n (%)**	**Abrocitinib 200mg OD (N=590) n (%)**	**All Abrocitinib (N=1198) n (%)**
Treatment-emergent adverse event (TEAE)	188 (55.0)	371 (61.0)	403 (68.3)	774 (64.6)
Serious adverse event (SAE)	11 (3.2)	19 (3.1)	11 (1.9)	30 (2.5)

Adverse event leading to study drug discontinuation	31 (9.1)	33 (5.4)	32 (5.4)	65 (5.4)

Overview of safety profile (All-Exposure Pool)

	Abrocitinib 100mg OD (N=885) n (%)	**Abrocitinib 200mg OD (N=1971) n (%)**	**All Abrocitinib (N=2856) n (%)**
Treatment-emergent adverse event (TEAE)	627 (70.8)	1420 (72.0)	2047 (71.7)
Serious adverse event (SAE)	48 (5.4)	74 (3.8)	122 (4.3)
Adverse event leading to study drug discontinuation	77 (8.7)	155 (7.9)	232 (8.1)

In the Primary Pool, there were more treatment-emergent adverse events (TEAEs) in the abrocitinib-treated groups compared to placebo. However, the proportion of patients reporting serious adverse events (SAEs), and adverse events (AEs) leading to discontinuation was similar or higher in the placebo group as compared to abrocitinib treatment groups. Among the patients reporting AEs, most had events that were mild or moderate (96%). The most frequent AEs overall (≥2% in any treatment group) that occurred more commonly in the abrocitinib groups than placebo were nausea (10.3% vs 2.0%), headache (6.8% vs 3.5%), acne (3.2% vs 0.0%), vomiting (2.3% vs 0.9%), herpes simplex (2.3% vs 0.9%), blood creatine phosphokinase increase (2.6 % vs 1.5%), and dizziness (2.3% vs 0.9%). The most frequent AEs reported in the All Exposure Pool were similar to those in the Primary Pool and majority of the events were mild or moderate (94%). There were 3 cases of deaths reported in the abrocitinib arm, all of which were not considered to be related to study treatment.

The AEs of special interest included serious infections (2.5 per 100 patient-years), malignancy (excluding non-melanoma skin cancer) (0.1 per 100 patient-years), venous thromboembolic events (VTE) (0.3 per 100 patient-years) and major adverse cardiovascular events (MACE) (0.2 per 100 patient-years). These were consistent with that known for JAK inhibitors and the proposed package insert has adequate warnings and precautions to mitigate the safety risks.

In general, abrocitinib presented an acceptable safety profile for the target patient population which was similar to that of other JAK inhibitors. Appropriate warnings and precautions have been included in the package insert to address the identified safety risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Atopic dermatitis is a chronically relapsing inflammatory skin disease that is characterized by pruritus, xerosis and eczematous lesions. Complications such as skin infections, can be debilitating and compromise the quality of life of patients. Local therapies such as topical corticosteroids may relieve the symptoms, however, systemic therapies may be required in moderate-to-severe AD patients who do not achieve adequate control with topical medications.

The clinical efficacy of abrocitinib was consistently demonstrated in 3 pivotal studies, where a statistically significant larger proportion of patients achieved both primary endpoints of IGA 0

or 1 and EASI-75 when compared with placebo at Week 12 or Week 16. These results were also supported by the key secondary endpoint in terms of significantly greater proportion of patients achieving at least a PP-NRS 4-point improvement compared with placebo. In the long-term extension study, improvements observed in the pivotal studies were maintained at Week 48.

The safety profile of abrocitinib was considered acceptable and similar to other JAK inhibitors. Common AEs were nausea, vomiting, headache, dizziness and the majority of AEs were mild or moderate in severity. Notable safety concerns of interest included infections, malignancy, VTE and MACE, which have been adequately addressed in the package insert.

Overall, the clinical benefits of abrocitinib for the treatment of moderate-to-severe AD whose disease cannot be adequately controlled with topical medications have been demonstrated to outweigh the risks associated with the treatment.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Cibinqo for the treatment of moderate-to-severe AD in adults who are candidates for systemic therapy and whose disease is not adequately controlled with topical medications or for whom topical treatments are otherwise medically inadvisable was deemed favourable and approval of the product registration was granted on 5 January 2022.

APPROVED PACKAGE INSERT AT REGISTRATION

This page is a placeholder for the approved PI if the Summary Report is to be published on the website.

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CIBINQO 50 mg film-coated tablets

Each film-coated tablet contains 50 mg abrocitinib.

CIBINQO 100 mg film-coated tablets

Each film-coated tablet contains 100 mg abrocitinib.

CIBINQO 200 mg film-coated tablets

Each film-coated tablet contains 200 mg abrocitinib.

Excipient with known effect

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

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

CIBINQO 50 mg film-coated tablets

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

CIBINQO 100 mg film-coated tablets

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

CIBINQO 200 mg film-coated tablets

Pink, oval tablet 18.42 mm long and 8.00 mm wide, debossed with “PFE” on one side and “ABR 200” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CIBINQO is indicated for the treatment of moderate-to-severe atopic dermatitis in adults (age 18 years and above) who are candidates for systemic therapy and whose disease is not adequately controlled with topical medications or for whom topical treatments are otherwise medically inadvisable.

4.2 Posology and method of administration

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

Posology

The recommended dose of CIBINQO is 100 mg once daily. An initial dose of 200 mg once daily for 12 weeks followed by maintenance with 100 mg once daily may be appropriate for some patients who need rapid relief of symptoms. The lowest effective dose for maintenance should be used (see Section 5.1).

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

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

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

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

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

Interruption of dosing may be needed for management of laboratory abnormalities as described in Table 1 (see Section 4.4).

Special dosage instructions

In patients receiving strong inhibitors of cytochrome P450 (CYP) 2C19 (e.g., fluvoxamine, fluconazole, fluoxetine and ticlopidine), the recommended dose of CIBINQO should be reduced by half to 100 mg or 50 mg once daily. The use of CIBINQO is not recommended concomitantly with moderate or strong inducers of CYP2C19/CYP2C9 enzymes (e.g., rifampin, apalutamide, efavirenz, enzalutamide, phenytoin) (see Section 4.5).

Renal impairment

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

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

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

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

Hepatic impairment
No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment (see Section 5.2). CIBINQO must not be used in patients with severe (Child Pugh C) hepatic impairment (see Section 4.3).

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

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

Method of administration

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

In patients who experience nausea 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

Active serious systemic infections, including tuberculosis (TB) (see Section 4.4).

Severe hepatic impairment (see Section 4.2).

Pregnancy and breast-feeding (see Section 4.6).

4.4 Special warnings and precautions for use

Serious infections

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

Treatment must not be initiated in patients with an active, serious systemic infection (see Section 4.3).

The risks and benefits of treatment with CIBINQO should be carefully considered prior to initiating in patients:

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

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

Tuberculosis
Patients should be screened for tuberculosis (TB) before starting CIBINQO therapy and consider yearly screening for patients in highly endemic areas for TB. CIBINQO must not be given to patients with active TB (see Section 4.3). For patients with a new diagnosis of latent TB or prior untreated latent TB, preventive therapy for latent TB should be started prior to initiation of CIBINQO.

Viral reactivation
Viral reactivation, including herpes virus reactivation (e.g., herpes zoster, herpes simplex), was reported in clinical studies (see Section 4.8). The rate of herpes zoster infections was higher in patients 65 years of age and older and patients with severe atopic dermatitis at baseline (see Section 4.8). If a patient develops herpes zoster, temporary interruption of treatment should be considered until the episode resolves.

Eczema herpeticum (disseminated viral infection mostly due to herpes simplex virus) was also reported in clinical studies with CIBINQO. The condition is characterised by rapid spread of vesicular and erosive lesions, fever and malaise inpatients with atopic dermatitis and requires prompt treatment with antiviral agents. Discontinuation or interruption of CIBINQO therapy until the resolution of an eczema herpeticum infection should be considered, depending on the seriousness of the event.

Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy and during therapy with CIBINQO. Patients with evidence of active hepatitis B or hepatitis C (positive hepatitis C PCR) infection were excluded from clinical

studies (see Section 5.2). Patients who were hepatitis B surface antigen negative, hepatitis B core antibody positive, and hepatitis B surface antibody positive had testing for hepatitis B virus (HBV) DNA. Patients who had HBV DNA above the lower limit of quantification (LLQ) were excluded. Patients who had HBV DNA negative or below LLQ could initiate treatment with CIBINQO; such patients had HBV DNA monitored. If HBV DNA is detected, a liver specialist should be consulted.

Vaccination

Use of live, attenuated vaccines during or immediately prior to CIBINQO therapy is not recommended. 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.

Venous thrombotic events including pulmonary embolism

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

Malignancy (including non-melanoma skin cancers)

Immunomodulatory drugs may increase the risk of malignancies including lymphoma. More cases of malignancies were observed with a JAK inhibitor other than CIBINQO compared with TNF inhibitors in the treatment of rheumatoid arthritis. Malignancies, including non-melanoma skin cancer (NMSC), were observed in clinical studies with CIBINQO. Clinical data are insufficient to assess the potential relationship of exposure to CIBINQO and the development of malignancies. Long-term safety evaluations are ongoing.

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 $<0.5 \times 10^3/mm^3$ and platelet count $<50 \times 10^3/mm^3$ were observed in less than 0.5% of patients in clinical studies. Treatment with CIBINQO should not be initiated in patients with a platelet count $<150 \times 10^3/mm^3$, an ALC $<0.5 \times 10^3/mm^3$, an ANC $<1 \times 10^3/mm^3$ or who have a haemoglobin value <8 g/dL (see Section 4.2). 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 CIBINQO (see Section 4.8). Lipid parameters should be assessed approximately 4 weeks following initiation of CIBINQO therapy and thereafter according to their risk for cardiovascular disease. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined. More serious cardiac adverse events have been observed with a JAK inhibitor other than CIBINQO compared with TNF inhibitors in the treatment of rheumatoid arthritis. Patients should be monitored and managed according to clinical guidelines, due to the known cardiovascular risks associated 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 population

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 4.8). There are no conclusive data in patients above 75 years of age and older.

Excipients

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

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicines to affect pharmacokinetics of abrocitinib

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

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

Co-administration with CYP2C19/CYP2C9 inducers
Administration of CIBINQO 200 mg after multiple doses with rifampin, a strong inducer of CYP enzymes, resulted in reduction of abrocitinib active moiety exposures by approximately 56% (see Section 4.2).

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

Co-administration with products which increase gastric pH
The effect of elevating gastric pH 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.

Potential for CIBINQO to affect pharmacokinetics of other medicines

No clinically significant effects of CIBINQO were observed in drug interaction studies with oral contraceptives (e.g., ethinyl oestradiol/levonorgestrel). *In vitro*, abrocitinib is an inhibitor of P glycoprotein (P-gp). Co-administration of dabigatran etexilate (a P-gp substrate), with a single dose of CIBINQO 200 mg increased dabigatran AUC_{inf} and C_{max} by approximately 53% and 40%, respectively, compared with administration alone. 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Women of childbearing potential

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

Breast-feeding

There are no data on the presence of 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.

Fertility

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

4.7 Effects on ability to drive and use machines

No studies have been conducted on the effect of CIBINQO on driving ability or ability to operate machinery. Patients should be informed that dizziness has been reported during treatment with CIBINQO (see Section 4.8).

4.8 Undesirable effects

Summary of safety profile

The most commonly reported adverse reactions occurring in ≥2% of patients treated with CIBINQO 200 mg in placebo-controlled studies are nausea (15.1%), headache (7.9%), acne (4.8%), herpes simplex (4.2%), blood creatine phosphokinase increased (3.8%), dizziness

(3.4%), and abdominal pain upper (2.2%). The most frequent serious adverse reactions are infections (0.3%) (see Section 4.4).

Tabulated list of adverse reactions

A total of 3,128 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 2 are adverse reactions observed in atopic dermatitis clinical studies presented by system organ class and frequency, using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2. Adverse reactions

System organ class	Very common	Common	Uncommon
Infections and infestations		Herpes simplex[a] Herpes zoster[b]	Pneumonia
Blood and lymphatic system disorders			Thrombocytopenia Lymphopenia
Metabolism and nutrition disorders			Hyperlipidaemia[c]
Nervous system disorders		Headache Dizziness	
Vascular disorders			Venous 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 thrombotic events include deep vein thrombosis.
e. Includes changes detected during laboratory monitoring (see text below).

Description of selected adverse reactions

Infections
In placebo-controlled studies, for up to 16 weeks, infections have been reported in 27.4% of patients treated with placebo and in 34.9% and 34.8% of patients treated with CIBINQO 100 mg and 200 mg, respectively. Most infections were mild or moderate. The percentage of

patients reporting infection-related adverse drug reactions in the 200 mg and 100 mg groups compared to placebo were: herpes simplex (4.2% and 2.8% vs 1.4%), herpes zoster (1.2% and 0.6% vs 0%), pneumonia (0.1% and 0.1% vs 0%). Herpes simplex was more frequent in patients with a history of herpes simplex or eczema herpeticum. Most of the herpes zoster events involved a single dermatome and were non-serious. 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 4.4).

In placebo-controlled studies, for up to 16 weeks, the rate of serious infections was 1.81 per 100 patient-years in patients treated with placebo, 3.32 per 100 patient-years in patients treated with CIBINQO 100 mg, and 1.12 per 100 patient-years in patients treated with CIBINQO 200 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 in patients treated with CIBINQO 100 mg and 2.33 per 100 patient-years in patients treated with CIBINQO 200 mg. The most commonly reported serious infections were herpes simplex, herpes zoster, and pneumonia (see Section 4.4).

Venous thrombotic events including pulmonary embolism
Among all patients treated with CIBINQO, including the long-term extension study, the rate of PE was 0.23 per 100 patient-years for 200 mg and 0 for per 100 patient-years for 100 mg. The rate of DVT was 0.23 per 100 patient-years in the 200 mg group and 0 per 100 patient-years in the 100 mg group (see Section 4.4).

Thrombocytopenia
In placebo-controlled studies, for up to 16 weeks, treatment was associated with a dose-related decrease in platelet count. Maximum effects on platelets were observed within 4 weeks, after which the platelet count returned towards baseline despite continued therapy. Confirmed platelet counts of $<50 \times 10^3/mm^3$ were reported in 0.1% of patients exposed to 200 mg, and in 0 patients treated with 100 mg or placebo. Among all patients exposed to CIBINQO, including the long-term extension study, confirmed platelet counts of $<50 \times 10^3/mm^3$ were reported in 0.1% 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 4.4).

Lymphopenia
In placebo-controlled studies, for up to 16 weeks, confirmed ALC $<0.5 \times 10^3/mm^3$ occurred in 0.3% of patients treated with 200 mg and 0% of patients treated with 100 mg or placebo. Both cases occurred in the first 4 weeks of exposure. Among all patients 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, most of whom were 65 years of age and older (see Section 4.4).

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% patients exposed to placebo (see Section 4.4).

Creatine phosphokinase elevations (CPK)
In placebo-controlled studies, for up to 16 weeks, significant increases in CPK values (>5 × ULN) occurred in 1.8% of patients treated with placebo, 1.8% of patients treated with 100 mg and 3.8% of patients treated with 200 mg of CIBINQO, respectively. 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% and 15.1% of patients treated with 100 mg and 200 mg, respectively. Discontinuation due to nausea occurred in 0.4% of patients treated with CIBINQO. Among patients with nausea, 63.5% of patients had onset of nausea in the first week of therapy. The median duration of nausea was 15 days. Most of the cases were mild to moderate in severity.

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

Adolescent population

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 4.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

CIBINQO is a Janus kinase (JAK)1 inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of haematopoiesis and immune cell function. 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.

Pharmacodynamic effects

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

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

Clinical efficacy and safety

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

Index (EASI) score ≥16, body surface area (BSA) involvement ≥10%, and Peak Pruritus Numerical Rating Scale (PP-NRS) ≥4 at baseline visit prior to randomisation. Patients who had a prior inadequate response or for whom topical treatments were medically unadvisable, or who had received systemic therapies were eligible for inclusion. All patients who completed the parent studies were eligible to enrol into the long-term extension study EXTEND.

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

Clinical response
12-week monotherapy (MONO-1, MONO-2) and 16-week TCS combination (COMPARE) studies
A significantly larger proportion of patients achieved both primary endpoints IGA 0 or 1 and/or EASI-75 with 100 mg or 200 mg once daily CIBINQO compared with placebo at Week 12 or Week 16 (see Table 3).

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

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

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

Table 3. Efficacy results of CIBINQO monotherapy at Week 12

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

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

a. IGA responders were patients with IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points.
b. EASI-75 responders were patients with ≥75% improvement in EASI from baseline.
c. CIBINQO in monotherapy.
d. Statistically significant with adjustment for multiplicity vs placebo.
e. Statistically significant without adjustment for multiplicity vs placebo.
f. Results shown are least squares mean change from baseline.

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

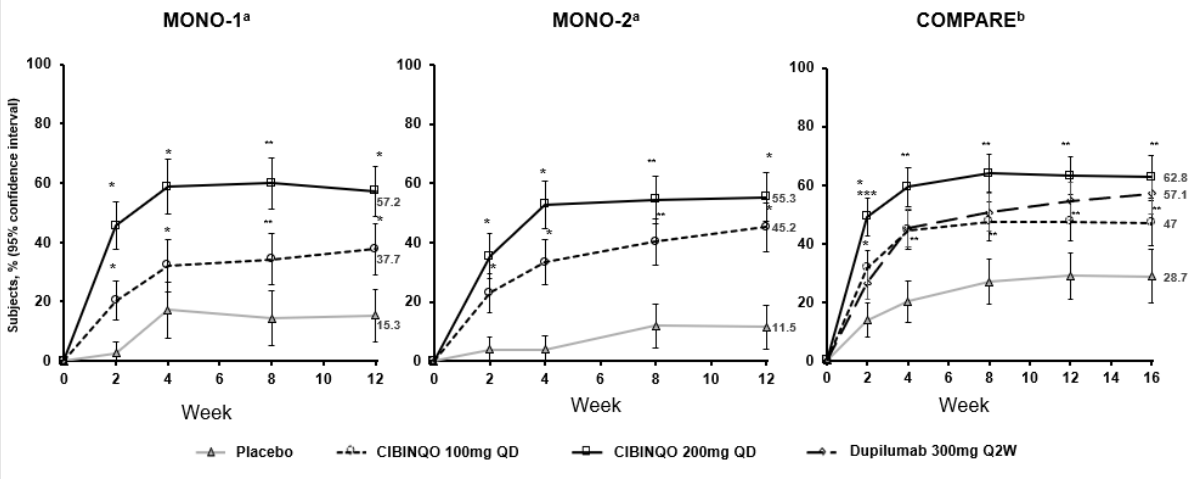
	COMPARE[c]							
	Week 12				Week 16			
	CBQ + topicals		PBO + topicals	DUP + topicals	CBQ + topicals		PBO + topicals	DUP + topicals
	200 mg N=226	100 mg N=238	N=131	N=243	200 mg N=226	100 mg N=238	N=131	N=243
	% Responders (95% CI)							
IGA 0 or 1[a]	48.4[d] (41.8, 55.0)	36.6[d] (30.4, 42.8)	14.0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

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

a. IGA responders were patients with IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points.
b. EASI-75 responders were patients with ≥75% improvement in EASI from baseline.
c. CIBINQO in combination with topical therapy.
d. Statistically significant with adjustment for multiplicity vs placebo.
e. Statistically significant without adjustment for multiplicity vs placebo.
f. Results shown are least squares mean change from baseline.

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

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



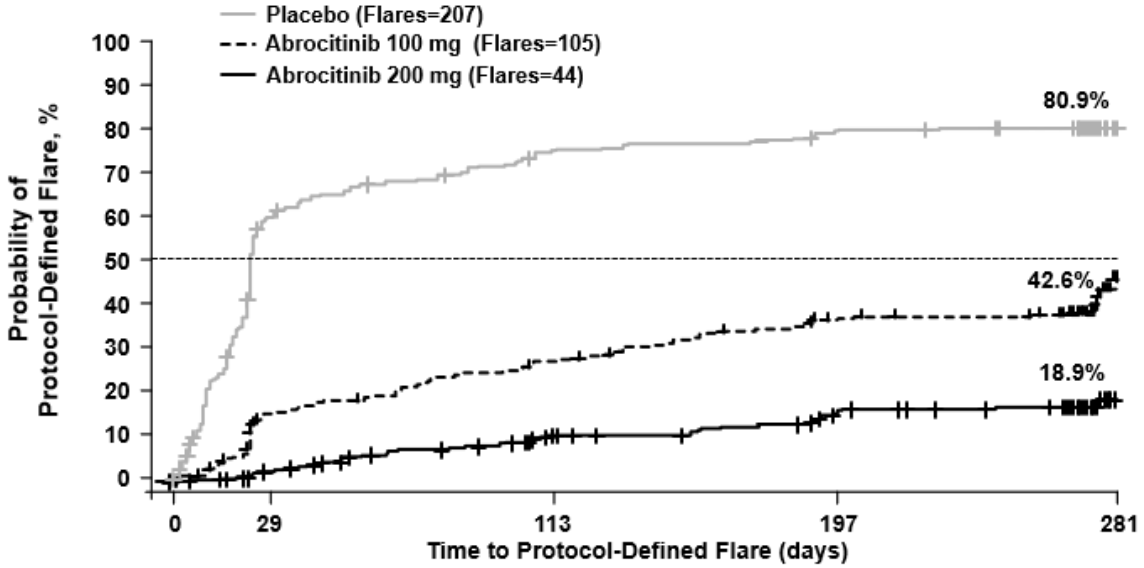
Abbreviations: PP-NRS=Peak Pruritus Numerical Rating Scale; QD=once daily.
PP-NRS4 responders were patients with ≥4-point improvement in Peak Pruritus Numerical Rating Scale (PP-NRS) from baseline.
a. CIBINQO used in monotherapy.
b. CIBINQO used in combination with medicated topical therapy.
* Statistically significant with adjustment for multiplicity vs placebo.
** Statistically significant without adjustment for multiplicity vs placebo.
*** Statistically significant with adjustment for multiplicity vs dupilumab.

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

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

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

Figure 2. Time to protocol-defined flare



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

Long-term efficacy
Eligible patients who completed the full treatment period of a qualifying parent study (e.g., MONO-1, MONO-2, COMPARE, REGIMEN) were considered for enrollment in the long-term extension study EXTEND. In EXTEND, patients received CIBINQO with or without background medicated topical therapy. Patients who were previously randomised to CIBINQO 100 mg or 200 mg once daily in parent studies continued the same dose in EXTEND as in the parent study, and the blind was maintained.

Among patients who achieved response after 12 weeks of treatment and entered EXTEND, the majority of patients maintained their response at Week 48 of cumulative treatment for both doses of CIBINQO [60% and 70% for IGA (0 or 1) response, 79% and 87% for EASI-75, and 62% and 83% for PP-NRS4 with 100 mg once daily and 200 mg once daily, respectively].

Among patients who did not achieve response after 12 weeks of treatment and entered EXTEND, a proportion of patients achieved late-onset response by Week 24 (from baseline) of continued treatment with CIBINQO [25% for IGA (0 or 1) response, and 50% and 59% for EASI-75 with 100 mg once daily and 200 mg once daily, respectively].

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

5.2 Pharmacokinetic properties

Absorption

Abrocitinib is well-absorbed with over 91% extent of oral absorption and absolute oral bioavailability of approximately 60%. The oral absorption of abrocitinib is rapid and peak plasma concentrations are reached within 1 hour. Both C_{max} and AUC of abrocitinib increased dose proportionally from 30 to 400 mg. Co-administration of CIBINQO with a high-fat meal had no clinically relevant effect on abrocitinib exposures (AUC and C_{max} increased by approximately 26% and 29%, respectively, and T_{max} was prolonged by 2 hours). In clinical studies, CIBINQO was administered without regard to food (see Section 4.2).

Distribution

After intravenous administration, the volume of distribution of 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.

Biotransformation

The *in vitro* metabolism of abrocitinib is mediated by multiple CYP enzymes, CYP2C19 (~53%), CYP2C9 (~30%), CYP3A4 (~11%) and CYP2B6 (~6%). In a human radiolabeled study, abrocitinib was the most prevalent circulating species, with 3 polar mono-hydroxylated metabolites identified as M1 (3-hydroxypropyl), M2 (2-hydroxypropyl), and M4 (pyrrolidinone pyrimidine). At steady state, M2 (11%) and M4 (24%) are major metabolites and M1 (9.6%) is a minor metabolite. Of the 3 metabolites in circulation, M1 and M2 have similar JAK inhibitory profiles as abrocitinib, while M4 was pharmacologically inactive. The pharmacologic activity of 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. 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. As a percent of total clearance, the renal elimination for M1 is 74% and >90% for M2 and M4, while the faecal elimination of M1, M2, and M4 are 8%, 4%, and 2% respectively.

Special populations

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

Adolescents (≥12 to <18 years)
Based on population pharmacokinetic analysis, the mean CIBINQO steady-state exposures in adolescent patients compared to adults at their typical body weights was not significantly different.

Paediatric (<12 years)
The pharmacokinetics of CIBINQO in paediatric patients under 12 years of age have not yet been established (see Section 4.2).

Renal impairment

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

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

Hepatic impairment

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

5.3 Preclinical safety data

General toxicity

In toxicity studies of up to 1 month of CIBINQO dosing in rats initiated at 6-8 weeks and 9-weeks of age, a bone dystrophy finding was noted, at exposure of greater than or equal to 22 times the human AUC at the maximum recommended human dose (MRHD) of 200 mg. No

bone findings were observed in rats at any dose in the 6-month toxicity study (up to 25 times the human AUC at the MRHD of 200 mg) or in any of the toxicity studies in cynomolgus monkeys (up to 30 times the human AUC at the MRHD of 200 mg).

Genotoxicity

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

Carcinogenicity

No evidence of tumorigenicity was observed in Tg.rasH2 mice administered CIBINQO for 26 weeks at exposures equal to 0.6 and 0.2 times the human AUC at the MRHD of 200 mg in female and male mice, respectively. In the 104-week oral carcinogenicity study, CIBINQO resulted in statistically higher incidence of benign thymomas in female rats at exposures greater than or equal to 2.7 times the human AUC at the MRHD of 200 mg. No evidence of CIBINQO-related tumorigenicity was observed following oral CIBINQO administration in female rats at exposures equal to 0.6 times the human AUC at the MRHD of 200 mg or in male rats at exposures equal to 13 times the human AUC at the MRHD of 200 mg.

Reproductive and developmental toxicity

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

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

In an embryo-foetal development study in pregnant rats, oral administration of CIBINQO during gestation days 6 to 17 resulted in increased embryo-foetal lethality at exposures equal to 16 times the human AUC at the MRHD of 200 mg. No embryo-foetal lethality was observed in pregnant rats orally dosed with CIBINQO during organogenesis at exposures equal to 10 times the human AUC at the MRHD of 200 mg. CIBINQO resulted in increased incidences of skeletal variations of short 13th ribs at exposures greater than or equal to 10 times the human AUC at the MRHD of 200 mg and reduced ventral processes, thickened ribs, and unossified metatarsals were observed at exposures equal to 16 times the human AUC at the MRHD of 200 mg. No skeletal variations were noted in rats at exposures equal to 2.3 times the human AUC at the MRHD of 200 mg.

In a 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 10 times the human AUC at the MRHD of 200 mg and lower postnatal survival at exposures equal to 16 times the human AUC at the MRHD of 200 mg. No maternal or developmental toxicity was observed in either dams or offspring at exposures equal to 2.3 times the human AUC at the MRHD of 200 mg.

Juvenile animal toxicity

In the juvenile rat study, oral administration of CIBINQO to rats initiated at postnatal Day 10 resulted in bone findings (malrotated and/or impaired use of the forelimbs, hindlimbs, or paws, fractures and/or abnormalities of the femoral head, and bony dystrophy), at exposures ≥0.8 times the human AUC at the MRHD of 200 mg. Irreversible low femur length and width were observed at exposures 26 times the human AUC at the MRHD of 200 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Dibasic calcium phosphate anhydrous
Sodium starch glycolate
Magnesium stearate

Film-coat

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Refer to outer carton.

6.4 Special precautions for storage

Keep in original package.

6.5 Nature and contents of container

CIBINQO 50 mg film-coated tablets

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

CIBINQO 100 mg film-coated tablets

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

CIBINQO 200 mg film-coated tablets

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. PRODUCT OWNER

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