PDL DRUG REVIEW

Proprietary Name: Cibinqo®
Common Name: abrocitinib
PDL Category: Anti-Inflammatories, Non-NSAID

Comparable Products	Preferred Drug List Status
Dupixent	Non-Preferred with Conditions
Elidel	Preferred with Conditions
Rinvoq	Non-Preferred with Conditions
Topical Corticosteroids	Preferred

Summary

Pharmacology/Usage: Abrocitinib, the active ingredient of Cibinqo®, is a Janus kinase (JAK) inhibitor. It reversibly inhibits JAK1 by blocking the adenosine triphosphate (ATP) binding site. In a cell-free isolated enzyme assay, abrocitinib was selective for JAK1 over JAK2, JAK3, and tyrosine kinase (TYK) 2, as well as the broader kinome. The relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known.

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.

Indication: For the treatment of adults with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. Cibinqo® is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants.

There is no pregnancy category for this medication; however, the risk summary indicates available data from pregnancies reported in clinical trials with Cibinqo® are not sufficient to establish a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcome. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Cibinqo® during pregnancy. Pregnant women exposed to Cibinqo® and healthcare providers are encouraged to call 1-877-311-3770. The safety and efficacy of use have not been established in pediatric patients less than 18 years of age.

Dosage Form: Film-Coated Tablets: 50mg, 100mg, 200mg. Swallow tablets whole with water; do not crush, split, or chew.

Recommended Dosage: Prior to starting Cibinqo®, perform the following tests and evaluations:

- Tuberculosis (TB) infection evaluation- Cibinqo® initiation is not recommended in patients with active TB. For patients with latent TB or those with a negative latent TB test who are at high risk for TB, start preventive therapy for latent TB prior to initiation of Cibinqo®.

- Viral hepatitis screening in accordance with clinical guidelines- Cibinqo® initiation is not recommended in patients with active hepatitis B or hepatitis C.
- A complete blood count (CBC)- Cibinqo® initiation is not recommended in patients with a platelet count <150,000/mm^3, an absolute lymphocyte count <500/mm^3, an absolute neutrophil count <1000/mm^3, or a hemoglobin value <8g/dl.

In addition, CBC evaluations are recommended not only at baseline, but 4 weeks after treatment initiation and 4 weeks after dosing increase of Cibinqo®. Laboratory evaluations may be extended for patients on chronic Cibinqo® therapy who develop hematological abnormalities.

Complete any necessary immunizations, including herpes zoster vaccinations, in agreement with current immunization guidelines prior to Cibinqo® initiation.

Take 100mg PO QD, with or without food, at about the same time each day. It can be used with or without topical corticosteroids. If an adequate response is not achieved with Cibinqo® 100mg QD after 12 weeks, consider increasing the dosage to 200mg PO QD. Discontinue therapy if inadequate response is seen after dosage increase to 200mg QD. If a dose is missed, administer the dose as soon as possible unless it is less than 12 hours before the next dose, in which case skip the missed dose. Thereafter, resume dosing at the regular scheduled time.

In patients who are known or suspected to be CYP2C19 poor metabolizers, the recommended dosage of Cibinqo® is 50mg QD. If an adequate response is not achieved with Cibinqo® 50mg QD after 12 weeks, consider increasing the dosage to 100mg PO QD. Discontinue therapy if inadequate response is seen after dosage increase to 100mg QD.

Dose adjustments are not required with mild renal impairment. Reduce the Cibinqo® dose to 50mg QD with moderate renal impairment. In subjects with mild and moderate renal impairment, if an adequate response is not achieved after 12 weeks, the dose of Cibinqo® can be doubled. Cibinqo® is not recommended for use in patients with severe renal impairment and end-stage renal disease including those on renal replacement therapy. Dose adjustment is not required with mild or moderate hepatic impairment; however, Cibinqo® is not recommended for use with severe hepatic impairment.

If a patient develops a serious or opportunistic infection, discontinue Cibinqo® and control the infection. The risks and benefits of treatment with Cibinqo® should be carefully considered prior to restarting therapy with Cibinqo®. Refer to the prescribing information regarding recommendations for Cibinqo® discontinuation for hematologic abnormalities.

Drug Interactions: Dosage reduction of Cibinqo® is recommended when co-administered with strong CYP2C19 inhibitors. In patients taking strong inhibitors of CYP2C19, reduce the dosage to 50mg QD. If an adequate response is not achieved with Cibinqo® 50mg QD after 12 weeks, consider increasing dosage to 100mg QD. Discontinue therapy if an inadequate response is seen after dosage increase to 100mg QD.

Avoid the concomitant use of Cibinqo® with drugs that are moderate to strong inhibitors of both CYP2C19 and CYP2C9.

Avoid the concomitant use of Cibinqo® with strong CYP2C19 or CYP2C9 inducers.

Monitor appropriately or dose titrate P-gp substrates where small concentration changes may lead to serious or life-threatening toxicities when co-administered with Cibinqo®.

Antiplatelet drugs, except for low-dose aspirin (≤81mg daily), during the first 3 months of treatment are contraindicated with Cibinqo®.

Avoid vaccination with live vaccines immediately prior to, during, and immediately after Cibinqo® therapy.

Box Warning: Cibinqo® has a box warning regarding serious infections, mortality, malignancy, major adverse cardiovascular events, and thrombosis.

- *Serious infections*- Patients treated with Cibinqo® may be at increased risk for developing serious infections that may lead to hospitalization or death; the most frequent serious infections reported with Cibinqo® were herpes simplex, herpes zoster, and pneumonia. If a serious or opportunistic infection develops, discontinue Cibinqo® and control the infection. Reported infections with JAK inhibitors used to treat inflammatory conditions include
    - Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Test for latent TB before and during therapy; treat latent TB prior to use. Monitor all patients for active TB during treatment, even patients with initial negative, latent TB test.
    - Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
    - Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.

  Avoid use of Cibinqo® in patients with an active, serious infection including localized infections. The risk and benefits of treatment with Cibinqo® should be carefully considered prior to starting treatment in patients with chronic or recurrent infections. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with Cibinqo®, including the possible development of TB in patients who tested negative for latent TB infection prior to starting therapy.
- *Mortality*- In a large, randomized, post-marketing safety study in RA patients 50 years of age and older with at least one cardiovascular risk factor comparing another JAK inhibitor to TNF blocker treatment, a higher rate of all-cause mortality, including sudden cardiovascular, was observed with the JAK inhibitor. Cibinqo® is not approved for use in RA patients.
- *Malignancies*- Malignancies were reported in patients treated with Cibinqo®. Lymphoma and other malignancies have been observed in patients receiving JAK inhibitors used to treat inflammatory conditions. In RA patients treated with another JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk.
- *Major Adverse Cardiovascular Events (MACE)*- MACE were reported in patients treated with Cibinqo®. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of MACE (defined as cardiovascular death, MI, and stroke), was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue Cibinqo® in patients that have experienced a MI or stroke.
- *Thrombosis*- Deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients treated with Cibinqo®. Thrombosis, including DVT, PE, and arterial thrombosis have been reported in patients receiving JAK inhibitors used to treat inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid Cibinqo® in patients at risk. If symptoms of thrombosis occur, discontinue Cibinqo® and treat appropriately.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Cibinqo® 200mg/100mg) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included nasopharyngitis (0.8%/4.5%), nausea (12.4%/3.9%), headache (4.3%/2.5%), herpes simples (2.4%/1.5%), increased blood creatinine phosphokinase (1.4%/0.8%), dizziness (2%/0.9%), urinary tract infection (1%/0.5%), fatigue (0.8%/1.1%), acne (4.7%/1.6%), vomiting (2.3%/0.6%), impetigo (0.2%/1.2%), oropharyngeal pain (0.4%/0.8%), hypertension (0.1%/0.5%), influenza (1.1%/1.2%), gastroenteritis (0.7%/0.5%), dermatitis contact (0.2%/0.8%), abdominal pain upper (1.9%/0.6%), abdominal discomfort (0.9%/0.2%), herpes zoster (1.2%/0.3%), and thrombocytopenia (1.5%/0%).

Perform periodic skin examination for patients who are at increased risk for skin cancer. Exposure to sunlight and UV light should be limited by wearing protective clothing and using broad-spectrum sunscreen.

Dose-dependent increase in blood lipid parameters were reported in patients treated with Cibinqo®. Lipid parameters should be assessed about 4 weeks following the start of Cibinqo® treatment and thereafter patients should be managed per clinical guidelines for hyperlipidemia. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Contraindications: In patients taking antiplatelet therapies, except for low-dose aspirin (≤81mg daily), during the first 3 months of treatment.

Manufacturer: Pfizer Laboratories Div. Pfizer Inc.

Analysis: The safety and efficacy of Cibinqo® as monotherapy and in combination with background topical corticosteroids (TCS) were assessed in 3 randomized, double-blind, placebo-controlled trials (Trial-AD-1, Trial-AD-2, and Trial-AD-3) that included subjects 12 years of age and older (N=1615) with moderate to severe atopic dermatitis as defined by the Investigator's Global Assessment (IGA) score ≥3, Eczema Area and Severity Index (EASI) score ≥16, body surface area (BSA) involvement ≥10%, and Peak Pruritus Numerical Rating Scale (PP-NRS) ≥4 at the baseline visit prior to randomization. (Note that Cibinqo® is not approved for use in pediatric patients.)

Overall, in the studies 53% were male, 69% were white, 64% had a baseline IGA score of 3 (moderate AD), and 36% had a baseline IGA score of 4 (severe AD). The baseline mean EASI score was 30. The baseline mean age of included subjects was 36 years, with 8% of subjects 12 to less than 18 years old and 92% of subjects 18 years of age and older. Subjects in these trials were those who had inadequate response to previous topical therapy or were subjects for whom topical treatments were medically inadvisable, or who had received systemic therapies including dupilumab. In each of the trials, greater than 40% had prior exposure to systemic therapy. Furthermore, in Trial-AD-1 and Trial-AD-2, 6% of the subjects had received dupilumab, whereas prior use of dupilumab was not allowed in Trial-AD-3.

The designs of the trial are presented in the table below, which was adapted from the prescribing information.

Study name	Population	Treatment Arms	Co-primary endpoints
Trial-AD-1 (Monotherapy), 12 weeks	≥12 yrs (N=387)	Cibinqo® 200mg PO QD Cibinqo® 100mg PO QD Placebo	IGA response week 12 EASI-75 week 12
Trial-AD-2 (Monotherapy), 12 weeks	≥12 yrs (N=391)	Cibinqo® 200mg PO QD Cibinqo® 100mg PO QD Placebo	
Trial AD-3 (Combination therapy), 16 weeks	≥18 yrs (N=837)	Cibinqo® 200mg PO QD Cibinqo® 100mg PO QD Placebo Dupilumab 300mg SC Q2W -all received background TCS	IGA response week 12 EASI-75 week 12

The clinical response for the monotherapy trials at week 12 are presented in the table below, which was adapted from the prescribing information. Note that IGA responders were subjects with IGA score of clear (0) or almost clear (1), on a 5-point scale, and a reduction from baseline of ≥2 points. EASI-75 responders were patients with ≥75% improvement in EASI from baseline.

	Trial-AD-1			Trial-AD-2		
	Cibinqo® 200mg (N=154)	Cibinqo® 100mg (N=156)	Placebo (N=77)	Cibinqo® 200mg (N=155)	Cibinqo® 100mg (N=158)	Placebo (N=78)
IGA 0 or 1	44%	24%	8%	38%	28%	9%
Difference from placebo	36%	16%	-	29%	19%	-

	Trial-AD-1			Trial-AD-2		
	Cibinqo® 200mg (N=154)	Cibinqo® 100mg (N=156)	Placebo (N=77)	Cibinqo® 200mg (N=155)	Cibinqo® 100mg (N=158)	Placebo (N=78)
NNT *per CHC*	3	7	-	4	6	-
EASI-75	62%	40%	12%	61%	44%	10%
Difference from placebo	51%	28%	-	50%	33%	-
NNT *per CHC*	2	4	-	2	4	-

The proportion of subjects achieving PP-NRS-4 at week 2 (defined as an improvement of ≥4 points from baseline in PP-NRS) was greater in subjects treated with Cibinqo® monotherapy 200mg QD (28% in Trial-AD-1 and 24% in Trial-AD-2) and 100mg QD (11% in both trials) compared to placebo (2% in both trials). A higher proportion of subjects in the Cibinqo® monotherapy 100mg or 200mg QD arm compared to placebo achieved improvement in itching at week 12.

The results of the combination trial that included Cibinqo® in combination with background topical corticosteroids, is presented in the table below, which was adapted from the prescribing information. Information on the dupilumab arm was not provided in the prescribing information.

	Trial-AD-3		
	Cibinqo® 200mg (N=226)	Cibinqo® 100mg (N=238)	Placebo (N=131)
IGA 0 or 1 at week 12	47%	36%	14%
Difference from placebo	34%	23%	-
NNT *per CHC*	3	5	-
EASI-75 at week 12	68%	58%	27%
Difference from placebo	41%	32%	-
NNT *per CHC*	3	4	-

The proportion of subjects achieving PP-NRS-4 at week 2 was higher in subjects treated with Cibinqo® 200mg (30%) and 100mg (14%) in combination with background medicated topical therapies compared with placebo (8%) in combination with background medicated topical therapies.

Place in Therapy: Cibinqo® is an oral Janus kinase (JAK) inhibitor indicated for the treatment of adults with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. Cibinqo® is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants. Cibinqo® has a box warning regarding increased risks of serious infections, mortality, malignancy, MACE, and thrombosis. Numerous drug interactions exist, and Cibinqo® is contraindicated in patients taking antiplatelet therapies, except for low-dose aspirin (≤81mg daily), during the first 3 months of treatment. The safety and efficacy of Cibinqo® were assessed and established in two monotherapy and one combination therapy trials.

In the full-text phase 3 study by Bieber et al[2] that compared abrocitinib plus topical therapies with placebo or dupilumab plus topical corticosteroids for the treatment of atopic dermatitis, the primary endpoints were the IGA response and EASI-75 response at week 12. Both doses of abrocitinib must have been significantly greater than placebo on the basis of both endpoints in order to have met the goal of the trial. The IGA response at week 12 for

abrocitinib and placebo were discussed above, while an IGA response at week 12 with dupilumab was reported in 88 of 241 patients (36.5%) in the dupilumab group. The second primary outcome of EASI-75 response at week 12 was reported in 140 of 241 patients (58.1%) in the dupilumab group. Abrocitinib was significantly more effective than placebo for IGA response ($p<0.001$ for both abrocitinib doses vs placebo) and for EASI-75 response ($p<0.001$ for both abrocitinib doses vs placebo). Itch response at week 2 occurred in 49.1% of the abrocitinib 200mg group, 31.8% in the abrocitinib 100mg group, 26.4% in the dupilumab group, and 13.8% in the placebo group. The weighted difference in the percentage of patients who had an itch response at week 2 between the abrocitinib 200mg group and the dupilumab group was 22.1 percentage points favoring abrocitinib 200mg ($p<0.001$). The weighted difference between the 100mg abrocitinib group and the dupilumab group was 5.2 percentage points ($p=0.20$), indicating no significant difference between the trial groups for this dose of abrocitinib.

There is some evidence at this time in a phase 3 study to suggest that Cibinqo® 200mg is significantly more effective than dupilumab with respect to itch response at week 2 and some evidence to suggest that Cibinqo® plus TCS is more effective than placebo plus TCS for primary endpoints of IGA response and EASI-75 response; however, there is no head-to-head evidence to suggest that it is safer or more effective than the other currently available, more cost-effective medications. Furthermore, the indication for Cibinqo® notes that its use is for patients not adequately controlled with other systemic drug products, including biologics (or when use of those therapies is inadvisable). It is therefore recommended that Cibinqo® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on other first line medications, as notated in prior authorization criteria.

PDL Placement:
- ☐ **Preferred**
- ☒ **Non-Preferred with Conditions**

References

[1] Cibinqo [package insert]. New York, NY: Pfizer Labs; 2022.

[2] Bieber T, Simpson EL, Silverberg JI, et al. Abrocitinib versus placebo or dupilumab for atopic dermatitis. *NEJM*. 2021; 384(12): 1101-1112.