PDL DRUG REVIEW

Proprietary Name: Kisqali®
Common Name: ribociclib
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Ibrance	Recommended with Conditions
Letrozole	Preferred

Summary

Pharmacology/Usage: Ribociclib, the active ingredient of Kisqali®, is a kinase inhibitor. It is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and play an important role in signaling pathways which lead to cell cycle progression and cellular proliferation.

Indications: In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

There is no pregnancy category with this medication; however, the risk summary indicates that based on findings from animal studies and its mechanism of action, Kisqali® can cause fetal harm when administered to a pregnant woman. There are no available human data informing the drug-associated risk. Females of reproductive potential should have a pregnancy test prior to starting treatment and should use effective contraception during treatment and for at least 3 weeks after the last dose. The safety and efficacy of use have not been established in the pediatric population.

Dosage Forms: Film-Coated Tablets: 200mg (equivalent to 254.40mg ribociclib succinate)

Recommended Dosage: Take 3 tablets (600mg) PO QD for 21 consecutive days with or without food followed by 7 days off treatment resulting in a complete cycle of 28 days. Coadminister with letrozole 2.5mg QD taken throughout the 28-day cycle. Both should be taken together, preferably in the morning. Refer to the prescribing information for dose modifications, dose interruptions, or discontinuation of treatment due to adverse events, such as with neutropenia, hepatobiliary toxicity, QT prolongation, or other toxicities.

Dose adjustments are not required in those with mild hepatic impairment; however, the recommended starting dose is 400mg QD for patients with moderate or severe hepatic impairment. Dose adjustments are not required with mild or moderate renal impairment, but effects are not known with severe renal impairment.

Drug Interactions: Avoid concomitant use of Kisqali® with drugs with a known potential to prolong QT such as antiarrhythmic medications (including but not limited to amiodarone, disopyramide, procainamide, quinidine, and sotalol), and other drugs that are known to prolong the QT interval (including but not limited to chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide, and ondansetron).

It is recommended to avoid the concomitant use of Kisqali® with a strong CYP3A4 inhibitor (e.g. boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, and voriconazole), and consider alternative concomitant medications with less potential for CYP3A inhibition. Pomegranates or pomegranate juice and grapefruit juice should be avoided as well. If concomitant use of Kisqali® with a strong CYP3A inhibitor cannot be avoided, reduce the dose of Kisqali® to 400mg QD.

Avoid concomitant use of strong CYP3A4 inducers with Kisqali® and consider an alternative concomitant medication with no or minimal potential to induce CYP3A (e.g. phenytoin, rifampin, carbamazepine, and St. John's wort).

Use caution when Kisqali® is administered with CYP3A substrates with a narrow therapeutic index. The dose of a sensitive CYP3A substrate with a narrow therapeutic index, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, may need to be reduced as ribociclib can increase their exposure.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Kisqali® plus letrozole) minus reported % incidence for placebo plus letrozole for all grades. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than its comparator.* The most frequently reported adverse events included urinary tract infection (3%), neutropenia (70%), leukopenia (32%), anemia (13%), lymphopenia (9%), decreased appetite (4%), headache (3%), insomnia (3%), dyspnea (3%), back pain (2%), nausea (23%), diarrhea (13%), vomiting (13%), constipation (6%), stomatitis (5%), abdominal pain (3%), alopecia (17%), rash (9%), pruritus (8%), fatigue (7%), pyrexia (7%), edema peripheral (2%), and abnormal liver function tests (12%). Reported laboratory abnormalities included leukocyte count decreased (64%), neutrophil count decreased (69%), hemoglobin decreased (31%), lymphocyte count decreased (29%), platelet count decreased (23%), alanine aminotransferase increased (10%), aspartate aminotransferase increased (12%), creatinine increased (14%), phosphorous decreased (9%), and potassium decreased (4%).

Kisqali® has been shown to prolong the QT interval in a concentration-dependent manner. There were no reported cases of Torsades de Pointes. It is recommended to assess ECG prior to starting treatment and to start treatment only in patients with QTcF values less than 450msec. Repeat ECG at about day 14 of the first cycle and the beginning of the second cycle, and then as clinically indicated. In addition, monitor serum electrolytes prior to starting treatment, at the beginning of the first 6 cycles, and as clinically indicated. Avoid the use of Kisqali® in patients who already have or who are at significant risk of developing QTc prolongation, including patients with long QT syndrome, uncontrolled or significant cardiac disease (including recent MI, CHF, unstable angina, and bradyarrhythmias), and electrolyte abnormalities. Avoid use with drugs known to prolong QTc interval and/or strong CYP3 inhibitors. Based on the observed QT prolongation during treatment, Kisqali® may require dose interruption, reduction or discontinuation. Refer to the prescribing information for additional information.

In a clinical trial, increases in transaminases were seen. It is thus recommended to perform liver function tests before starting Kisqali® treatment and to monitor liver function tests every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated. Per the severity of transaminase elevations, dose interruption, reduction, or discontinuation of Kisqali® may be required.

Contraindications: There are currently no contraindications listed with this product.

Manufacturer: Novartis Pharmaceuticals

Analysis: There was one randomized, double-blind, placebo-controlled study performed to assess the safety and efficacy of Kisqali® plus letrozole versus placebo plus letrozole in postmenopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease (N=668).

Women were stratified per the presence of liver and/or lung metastases. The median age was 62 years, with 45% older than 65 and 82% being white.

The main efficacy outcome was the investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST). Included results are from a pre-planned interim efficacy analysis of PFS, and results were consistent across patient subgroups of prior adjuvant or neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone-only metastatic disease. The PFS assessment per a blinded independent central radiologic review was consistent with investigator assessment. At the time of PFS analysis, 6.5% of patients died, and overall survival data were immature. The table below, adapted from the prescribing information, illustrates the results.

Endpoint	Kisqali® & letrozole	Placebo & letrozole
Progression-free survival (PFS)	N=334	N=334
Events	93 (27.8%)	150 (44.9%)
Median, months	Not reached	14.7
Hazard Ratio, p-value	0.556, p<0.0001	
Overall Response Rate	N=256	N=245
Patients with measurable disease	52.7	37.1

Place in Therapy: Kisqali® is indicated to be used in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. It has been shown to prolong the QT interval in a concentration-dependent manner, and thus laboratory assessments need to be performed prior to starting use and periodically throughout treatment. Results from a pre-planned interim analysis of PFS suggested that that Kisqali® plus letrozole was significantly more effective than placebo plus letrozole, with median months of PFS not reached by Kisqali®.

It is recommended that Kisqali® be placed on the recommended list with conditions to allow verification of appropriate diagnosis and concomitant use with letrozole.

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

References

[1] Kisqali [package insert]. East Hanover, NJ: Novartis Pharmaceuticals; 2017.