CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 July – August

BRAND NAME
Kisqali®

GENERIC NAME
ribociclib

MANUFACTURER
Novartis

DATE OF APPROVAL
March 13, 2017

PRODUCT LAUNCH DATE
March 14, 2017

REVIEW TYPE

☒ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☐ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastics, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Reviews for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)
Kisqali is indicated 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.

OFF-LABEL USES
Not applicable

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CLINICAL EFFICACY[1,2]

The study that established the efficacy of Kisqali for its FDA-approved indication was a randomized, double-blind, placebo-controlled, multicenter trial (MONALEESA-2) which included 668 postmenopausal women with HR-positive, HER2-negative, advanced breast cancer who had received no prior therapy for advanced disease.

Patients were equally randomized to receive either Kisqali 600 mg or placebo orally once daily for 21 consecutive days followed by 7 days off, together with letrozole 2.5 mg orally once daily for 28 days until disease progression, unacceptable toxicity, death, or discontinuation of Kisqali or letrozole for any other reason. Study patients had a median age of 62 years (range 23 to 91) and 45% of patients were older than 65. All patients had an ECOG performance status of 0 or 1. Other relevant baseline characteristics were comparable between groups. A total of 47% of patients had received chemotherapy and 51% had received anti-hormonal therapy in the neoadjuvant or adjuvant setting. The disease-free interval at baseline was more than 24 months in 397 patients (59.4%).

The primary endpoint was investigator-assessed progression-free survival (PFS). Secondary endpoints included overall survival (OS) and overall response rate (ORR). Results from a pre-planned interim efficacy analysis are as follows:

- Median duration of PFS was not reached in the Kisqali group (95% CI, 19.3- not reached) vs. 14.7 months (95% CI, 13.0-16.5) for placebo (HR, 0.56; 95% CI, 0.43-0.72; p = 3.29×10^{-6});
- After 12 months, the PFS rate was 72.8% (95% CI, 67.3-77.6) for Kisqali vs. 60.9% (95% CI, 55.1-66.2) for placebo;
- After 18 months, the PFS rate was 63.0% (95% CI, 54.6-70.3) for Kisqali and 42.2% (95% CI, 34.8-49.5) for placebo;
- The ORRs were 52.7% and 37.1% for Kisqali and placebo, respectively, among patients with measurable disease (p<0.001);
- OS results were immature at the time of the interim analysis, with 43 deaths (23 for Kisqali and 20 for placebo; the study remains blinded for follow-up of OS).

CONTRAINDICATIONS

None

BLACK BOX WARNINGS

None

DRUG INTERACTIONS

- Avoid co-administration of Kisqali with:

  - Strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, voriconazole, grapefruit juice);
  - Strong CYP3A inducers (e.g., phenytoin, rifampin, carbamazepine and St John's Wort (Hypericum perforatum));
  - Drugs that prolong the QT interval (e.g., amiodarone, disopyramide, procainamide, quinidine and sotalol, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide and intravenous ondansetron).
- If co-administration of Kisqali with a strong CYP3A inhibitor cannot be avoided, reduce the dose of Kisqali to 400 mg once daily;
- Caution is recommended when Kisqali is co-administered with CYP3A substrates with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus). The CYP3A substrate dose may need to be reduced.

ADVERSE REACTIONS

The most common adverse reactions (reported at a frequency ≥ 20%) were neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache and back pain.

The most common Grade 3/4 adverse reactions (reported at a frequency > 2%) were neutropenia, leukopenia, abnormal liver function tests, lymphopenia, and vomiting.

Dose reductions due to adverse reactions (ARs) occurred in 45% of patients receiving Kisqali plus letrozole and in 3% of patients receiving placebo plus letrozole. Permanent discontinuations due to ARs were reported in 7% of patients receiving Kisqali plus letrozole and 2% in patients receiving placebo plus letrozole. The most common ARs leading to treatment discontinuation of Kisqali in patients receiving Kisqali plus letrozole were increased ALT (4%) and AST (3%), and vomiting (2%).

Kisqali prolongs the QT interval in a concentration-dependent manner, with an estimated mean increase in QTc interval exceeding 20 ms at the mean steady-state C_{max} following administration of 600 mg once daily. In the MONALEESA-2 trial, one patient (0.3%) had >500 msec post-baseline QTcF value (average of triplicate), and nine patients (3%) had a >60 msec increase from baseline in QTcF intervals (average of triplicate). These ECG changes occurred within the first four weeks of treatment and were reversible with dose interruption. There were no reported cases of torsades de pointes. Syncope occurred in 9 patients (2.7%) in the Kisqali plus letrozole arm versus 3 (0.9%) in placebo plus letrozole arm. In the Kisqali plus letrozole treatment arm, there was one sudden death in a patient with Grade 3 hypokalemia and Grade 2 QT prolongation.

Baseline and repeat ECGs are recommended in the package labeling, along with monitoring of serum electrolytes. Kisqali should be initiated only in patients with QTcF values less than 450 msec at baseline and after correction of any serum electrolyte abnormalities.

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DOSAGE AND ADMINISTRATION
Kisqali is dosed as 600 mg taken orally once daily for 21 consecutive days followed by 7 days off treatment resulting in a complete cycle of 28 days. Kisqali is to be co-administered with an aromatase inhibitor taken once daily throughout the 28-day cycle.

PRODUCT AVAILABILITY
Tablets: 200 mg

THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
Ibrance (palbociclib)	125 mg PO QD for 21 consecutive days followed by 7 days off, in combination with an aromatase inhibitor	Used in combination with an aromatase inhibitor.

Boldface indicates generic availability

Utilization Management Recommendation
• There is not significant potential for inappropriate use. • Requiring utilization management to prevent potential off-label usage would be clinically appropriate.   o Recommended utilization management tool: prior authorization • It would be clinically appropriate to require a quantity limit.
Product Comparison
• CPAC score: 44 vs. Ibrance – May be used under unique circumstances • It would be clinically appropriate to provide equal access to Ibrance and Kisqali or to prefer Ibrance over Kisqali. • It would not be clinically appropriate to use Kisqali after a trial of Ibrance and vice versa because both drugs are indicated for first line treatment.

REFERENCES

[1] Kisqali Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2017; Available at: https://www.kisqali.com/. Accessed March 2017.
[2] Hortobagyi GN, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med* 2016;375:1738-48.