Adding KISQALI, CBC/LFT, and ECG to an Appropriate Treatment Plan and Creating a BPA for Appropriate Treatment Monitoring

Epic® Beacon

Maintaining up-to-date protocols in EHRs is an integral part of providing comprehensive, consistent care. To better support your health care institution, Novartis has developed this Epic EHR Guide that can be used by your EHR support or information technology departments to develop, configure, and modify EHR components relevant to treatment with KISQALI.

Introduction

This guide provides an overview of how to add KISQALI, CBC/LFT, and ECG to an appropriate treatment plan and create a BPA for appropriate treatment monitoring within the Epic EHR. KISQALI monitoring and dosing information is also included for reference. The navigation tabs at the top of each page can be used to easily navigate between information.

BPA=Best Practice Alert; CBC=complete blood count; ECG=electrocardiogram; EHR=Electronic Health Record; LFT=liver function test.

Indications

KISQALI is indicated for the treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer (mBC) in combination with:

- an aromatase inhibitor as initial endocrine-based therapy; or
- fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy

IMPORTANT SAFETY INFORMATION

Interstitial lung disease/pneumonitis. Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with KISQALI and other CDK4/6 inhibitors.

In patients with advanced or mBC (MONALEESA-2, MONALEESA-3, MONALEESA-7), 1.6% of patients had ILD/pneumonitis of any grade, 0.4% had grade 3/4, and 0.1% had a fatal outcome. Additional cases of ILD/pneumonitis have occurred in the postmarketing setting, some resulting in death.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis, which may include hypoxia, cough, and dyspnea. In patients who have new or worsening respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt KISQALI immediately and evaluate the patient. Permanently discontinue KISQALI in patients with severe ILD/pneumonitis or any recurrent symptomatic ILD/pneumonitis.

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Upfront ECG Monitoring

ECG and QTcF Prolongation Overview

- **ECG** measures electrical impulses as 5 waves using the letters P, Q, R, S, and T[1]
- **QT interval** is the space between the start of the Q wave and end of the T wave, characterizing the electrical depolarization and repolarization of the heart's ventricles[1,2]
- **QTc** is a QT interval measurement corrected to compare QT intervals at different heart rates[2]
- **QTcF** is a QT interval corrected using the Fridericia formula[3]
- **Prolongation of the QTc interval** is a risk factor of developing torsades de pointes or other clinically significant arrhythmias[4]
- **Risk factors for QT interval prolongation** include medications with risk of lengthening the QT interval, 4 electrolyte imbalances (hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia), age, sex, bradycardia, and family/personal medical history[4-6]

KISQALI QTcF Prolongation Incidence[3]

Low incidence of QT prolongation across all KISQALI clinical trials, and most cases were moderate in nature

In a pooled analysis across 3 phase III trials of 1054 premenopausal and postmenopausal patients treated with KISQALI + an AI or fulvestrant:

1% had a >500 ms post baseline QTcF value

6% experienced a >60 ms increase from baseline in QTcF interval

- There were no reported cases of torsades de pointes

ECG changes were reversible with dose interruption and the majority occurred within the first 4 weeks of treatment.

AI=aromatase inhibitor.

IMPORTANT SAFETY INFORMATION (continued)

Severe cutaneous adverse reactions. Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with KISQALI.

If signs or symptoms of SCARs occur, interrupt KISQALI until the etiology of the reaction has been determined. Early consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management.

If SJS, TEN, or DiHS/DRESS is confirmed, permanently discontinue KISQALI. Do not reintroduce KISQALI in patients who have experienced SCARs or other life-threatening cutaneous reactions during KISQALI treatment.

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Upfront ECG Monitoring (continued)[3]

ECG Monitoring		
Baseline		✓
Cycle 1	Day 14	✓

- KISQALI should only be initiated in patients with QTcF <450 ms. In case of QTcF prolongation during therapy, more frequent monitoring is recommended
- Any additional monitoring should be performed as clinically indicated
- Monitoring requirements based on a 28-day treatment cycle

Only 2 ECGs are required—and all are completed within the first 15 days of treatment.

IMPORTANT SAFETY INFORMATION (continued)

QT interval prolongation. KISQALI has been shown to prolong the QT interval in a concentration-dependent manner.

Avoid KISQALI in patients who are at significant risk of developing torsades de pointes (TdP), including those with:

- congenital long QT syndrome;
- uncontrolled or significant cardiac disease, recent myocardial infarction, heart failure, unstable angina, bradyarrhythmias, uncontrolled hypertension, high degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism;
- electrolyte abnormalities;
- taking drugs known to prolong QT interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval.

Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction, or discontinuation.

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Routine Laboratory Monitoring[3]

		CBC/LFT	Electrolytes
Baseline		✓	✓
Cycle 1	Day 14	✓	
Cycle 2	Day 1	✓	✓
	Day 14	✓	
Cycle 3-6	Day 1	✓	✓

- For LFTs, if grade ≥2 abnormalities are noted, more frequent monitoring is recommended
- Correct any electrolyte abnormalities prior to treatment
- Additional monitoring may be required as clinically indicated
- Monitoring requirements based on a 28-day treatment cycle

The majority of scheduled monitoring occurs within the first 2 cycles of therapy and there is no scheduled monitoring beyond Cycle 6.

IMPORTANT SAFETY INFORMATION (continued)

QT interval prolongation (continued). In patients with advanced or mBC (MONALEESA-2, MONALEESA-3, and MONALEESA-7) who received 600 mg KISQALI plus NSAI or fulvestrant, 15 of 1054 patients (1.4%) had >500 ms postbaseline QTcF value, and 61 of 1054 (6%) had a >60 ms QTcF increase from baseline. QTcF prolongation was reversible with dose interruption. The majority of QTcF prolongation occurred within the first 4 weeks of KISQALI. There were no reported cases of torsades de pointes. In MONALEESA-2, in the KISQALI + letrozole treatment arm, there was 1 (0.3%) sudden death in a patient with grade 3 hypokalemia and grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3.

Perform electrocardiogram (ECG) in all patients prior to starting KISQALI. Initiate treatment with KISQALI only in patients with QTcF values <450 ms. Repeat ECG at approximately Day 14 of the first cycle and as clinically indicated.

Monitor serum electrolytes (including potassium, calcium, phosphorus, and magnesium) prior to the initiation of KISQALI, at the beginning of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting KISQALI.

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Monitoring Summary[3]

		Upfront ECG Monitoring	Routine Laboratory Monitoring	
		ECG Monitoring	CBC/LFT	Electrolytes
Baseline		✓	✓	✓
Cycle 1	Day 14	✓	✓	
Cycle 2	Day 1		✓	✓
	Day 14		✓	
Cycle 3-6	Day 1		✓	✓

LAB The majority of scheduled monitoring occurs **within the first 2 cycles of therapy** and there is **no scheduled monitoring beyond Cycle 6**.

ECG **Only 2 ECGs are required**—and all are completed within the **first 15 days of treatment**.

IMPORTANT SAFETY INFORMATION (continued)

Increased QT prolongation with concomitant use of tamoxifen. KISQALI is not indicated for concomitant use with tamoxifen. Avoid use of tamoxifen with KISQALI. In MONALEESA-7, the observed mean QTcF increase from baseline was >10 ms higher in the tamoxifen + placebo subgroup compared with the nonsteroidal aromatase inhibitor (NSAI) + placebo subgroup. In the placebo arm, an increase of >60 ms from baseline occurred in 6/90 (7%) of patients receiving tamoxifen, and in no patients receiving an NSAI. An increase of >60 ms from baseline in the QTcF interval was observed in 14/87 (16%) of patients in the KISQALI and tamoxifen combination and in 18/245 (7%) of patients receiving KISQALI plus an NSAI.

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mBC Dosing

KISQALI—the only CDK4/6 inhibitor that offers one tablet strength for simple dose reductions

Recommended Dosing for mBC Indication

3  **tablets (600 mg)**

1st reduction

2  **tablets (400 mg)**

2nd reduction

1  **tablet (200 mg)**

- KISQALI is given as 600 mg (3 x 200-mg tablets) orally once daily (3 weeks on, 1 week off) with either:
  - An AI once daily (continuously); in premenopausal patients and men, an LHRH agonist should be administered according to current clinical practice guidelines; or
  - Fulvestrant 500 mg intramuscularly on Days 1, 15, and 29, and once monthly thereafter for postmenopausal patients or men. In male patients, an LHRH agonist should be administered according to current clinical practice guidelines
- Dose adjustments for adverse reactions should be made in a stepwise order by reducing the number of tablets taken
- Dose modification of KISQALI is recommended based on individual safety and tolerability
- If dose reduction below 200 mg/day is required, discontinue treatment
- KISQALI can be taken with or without food

Simple dose reductions with no need for a new prescription or additional cost to patient mid-cycle.

LHRH=luteinizing hormone-releasing hormone.

IMPORTANT SAFETY INFORMATION (continued)

Hepatotoxicity. In patients with advanced or mBC, drug-induced liver injury and increases in transaminases occurred with KISQALI.

In patients with advanced or mBC (MONALEESA-2, MONALEESA-7, and MONALEESA-3) treated with KISQALI, grade 3 or 4 increases in ALT and AST occurred in 11% and 8%, respectively. Among the patients who had grade ≥3 ALT/AST elevation, the median time to onset was 92 days for the KISQALI plus aromatase inhibitor or fulvestrant treatment arms. The median time to resolution to grade ≤2 was 21 days in the KISQALI plus aromatase inhibitor or fulvestrant treatment arms. In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST >3x the ULN and total bilirubin >2x the ULN, with normal alkaline phosphatase, in the absence of cholestasis (Hy's Law) occurred in 6 (1%) patients and all patients recovered after discontinuation of KISQALI.

Perform liver function tests (LFTs) before initiating KISQALI. Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation.

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EHR Build Guide: Adding KISQALI, CBC/LFT, and ECG to an Appropriate Treatment Plan

- Based on clinician's need, the analyst will build out the PRL (protocol) and include all necessary pretreatment cycles and regimen cycles
- Work in collaboration with Willow/Pharmacy for eRx medication deliverables
  - Add into to the appropriate cycles
  - Standard meds should be built ahead to streamline PRL build process (eg, KVO/Flushes order group and Pre-Meds order group with med options such as Dexamethasone/DECADRON®)

Pretreatment Cycle

Step 1: Appointment Request Procedure

- This is an appointment request to go over the fundamentals of the protocol study and what the patient can expect/learn about chemotherapy before moving forward

Step 2: OP Pharmacotherapy Referral

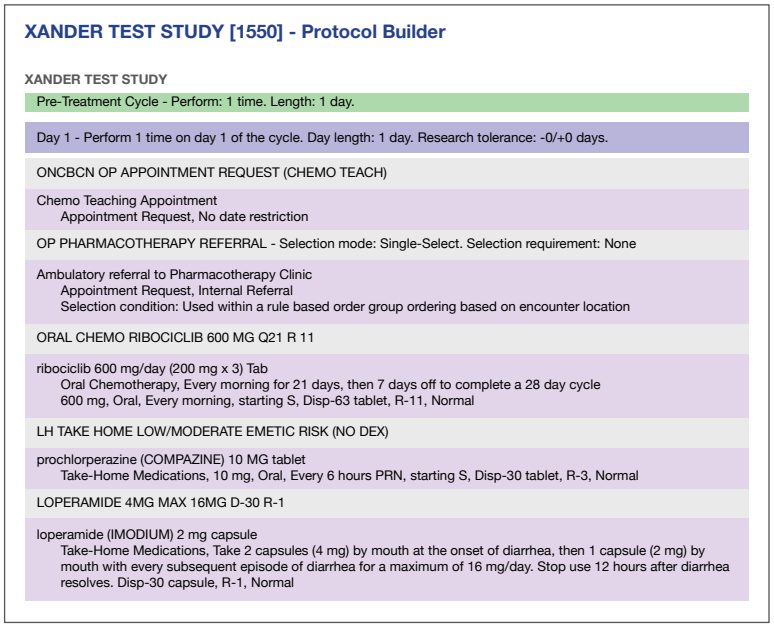
- Order Group housing the Ambulatory referral to Pharmacotherapy Clinic (Internal Referral for organization to keep track of encounter and scheduling)

Step 3: Oral Chemo Ribociclib aka KISQALI

- Oral chemo regimen may start in the pretreatment cycle here with a take-home prescription oral chemo with instructions

Step 4: Take Home Low/Moderate Emetic Risk (No Dex)

- This Order Grouper is a standard grouper built out with Low/Moderate Emetic in this case COMPAZINE®
- In early stages of Build/Implementation, the analyst and shareholders should develop a plan for standardizing Low, Medium, and High Emetic Risk Order Groupers with the appropriate meds/med options (can be configured to include multiple and single select options)



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IMPORTANT SAFETY INFORMATION (continued)

Neutropenia. KISQALI causes concentration-dependent neutropenia. In patients with advanced or mBC (MONALEESA-2, MONALEESA-7, and MONALEESA-3) who received KISQALI plus NSAI or fulvestrant, 75% had neutropenia, 62% had grade 3/4 decrease in neutrophil count (based on laboratory findings), and 1.7% had febrile neutropenia. The median time to grade ≥2 neutropenia was 17 days. The median time to resolution of grade ≥3 neutropenia to grade <3 was 12 days. Treatment discontinuation due to neutropenia was required in 1% of patients.

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EHR Build Guide: Adding KISQALI, CBC/LFT, and ECG to an Appropriate Treatment Plan (continued)

Cycle 1

Step 1: ONCBCN OP APPT REQUEST

- Standard OSQ with Outpatient Oncology Beacon appointment procedure for in-clinic infusion

Step 2: ONCBCN OP APPT REQUEST (PHARMACIST FOLLOW-UP TELEVISIT)

- Standard Outpatient Appt request to schedule a follow up with Pharmacist via Tele-Visit (Zoom)
- Since KISQALI is an Oral Chemo prescription take-home medication (outpatient prescription) the pharmacist will set up the Tele-Visit to check in with patient

Step 3: ONCBCN OP LABS (CBC W ANC/OMP)

- Standard OSQ grouper with labs attached

Step 4: ECG 12 Lead Procedure

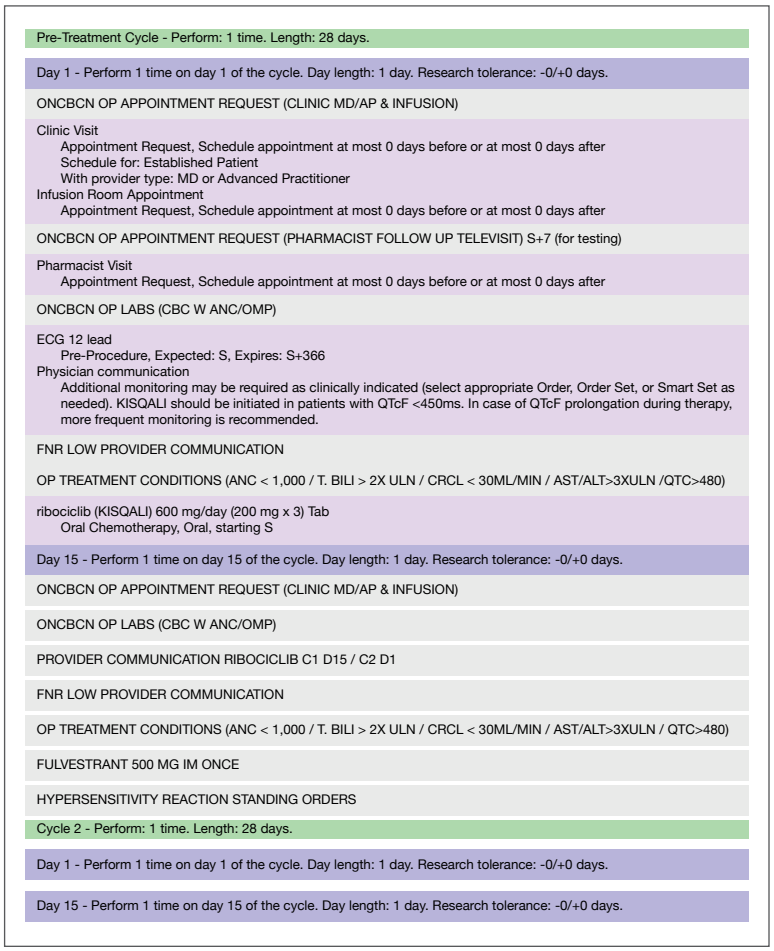
- Add in basic echocardiogram procedure order here after the OP LABS standard Order Grouper (OSQ) to show flexibility analyst has to add in specific orders on a Cycle and Day basis for clinicians

Step 5: Add Physician Communication With Further Study Instructions and ECG Use

- Consider putting Physician/Nursing/Pharmacist Communications within the protocol build so that the end-user is informed before signing and releasing days orders

Step 6: PROVIDER COMMUNICATION RIBOCICLIB

- Another OSQ Order Grouper that is explicitly labeled Physician/Provider Communication
- Physician communication provides in-depth instructions for dispensation, documentation, and baseline levels for patient observation



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IMPORTANT SAFETY INFORMATION (continued)

Neutropenia (continued). Perform complete blood count (CBC) before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction, or discontinuation.

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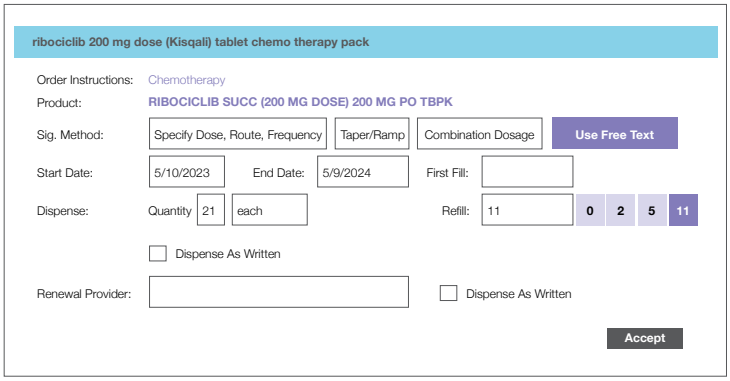
EHR Build Guide: Creating a BPA for Appropriate Treatment Monitoring

BPA Setup for KISQALI Treatment Monitoring

- The following information provides an overview for how a cancer center that wants to implement a BPA for their patients taking KISQALI would do so. The example used in this overview highlights how one would create a BPA for patients prescribed KISQALI but do not have appropriate baseline testing placed.
- Minimum Required Version of Epic: This guide assumes that the organization is using the Epic 2017 version or later
- Build Complexity: Low (from 1 day to 1 week)



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Base Criteria—Build Process Overview

Step 1. Create a BPA criteria record.

Step 2. Create a BPA base record.

Base Criteria—Detailed Build Instructions

In Hyperspace, follow the path:

Step 1. Epic button

Step 2. Tools

Step 3. Management Console

Step 4. Decision Support

Step 5. Best Practice Advisory

IMPORTANT SAFETY INFORMATION (continued)

Embryo-fetal toxicity. Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose.

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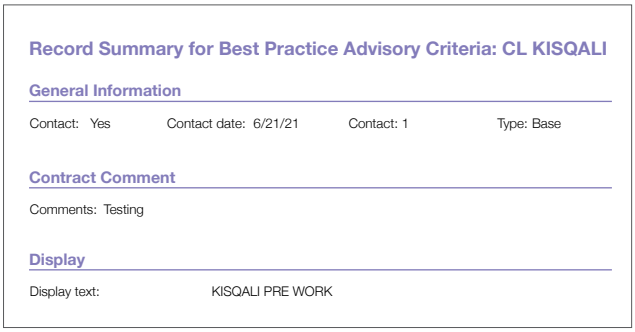
EHR Build Guide: Creating a BPA for Appropriate Treatment Monitoring (continued)

Base Criteria—Detailed Build Instructions (continued)

Step 1: Create a BPA criteria record

Create a BPA record for "PRE-TESTING for KISQALI Patients" (according to the organization's naming convention) of record type Criteria with the following settings:

- On the Contact Comment and Display pages, enter any additional information explaining the purpose of the criteria as well as the Display text you would like to see on your BPA
- On the Contact Comment page, click the Released checkbox to indicate that the BPA Criteria record is available for use


Record Summary for Best Practice Advisory Criteria: CL KISQALI

General Information

Contact: Yes Contact date: 6/21/21 Contact: 1 Type: Base

Contract Comment

Comments: Testing

Display

Display text: KISQALI PRE WORK

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Step 2: Create a BPA base record

The BPA base record contains the logic for when to display the alert, the display text in the alert for the clinician, where in the chart the alert appears, and appropriate follow-up actions. The triggering action for the BPA **is an order for KISQALI**.

- Create a BPA record for "TESTING REQUIREMENTS FOR KISQALI Patients" (according to your organization's naming convention) of record type Base with the following settings:
  - On the Contact Comment and Display pages, enter the following:
    - > Display Text: "Pre-Workup and ongoing monitoring is required."
    - > Display to user: YES to display in workflows such as the storyboard, general BPA sections, and via chart review
    - > Include links to guidelines if requested by cancer center clinicians
  - On the Restrictions page, enter any encounter filtering restrictions under the **INCLUDE ENCOUNTER RESTRICTION**

Notes

- The Customers (ie, physician, medical group, integrated delivery network [IDN]) shall be solely responsible for implementation, testing, and monitoring of the instructions to ensure proper orientation in each customer's EHR system
- Capabilities, functionality, and setup (customization) for each individual EHR system vary. Novartis shall not be responsible for revising the implementation instructions it provides to any Customer in the event that Customer modifies or changes its software, or the configuration of its EHR system, after such time as the implementation instructions have been initially provided by Novartis
- While Novartis tests its implementation instructions on multiple EHR systems, the instructions are not guaranteed to work for all available EHR systems and Novartis shall have no liability thereto
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IMPORTANT SAFETY INFORMATION (continued)

Laboratory abnormalities. Across clinical trials of patients with advanced or metastatic breast cancer, the most common laboratory abnormalities reported in the KISQALI arm (all grades, pooled incidence ≥20%) **were leukocytes decreased, neutrophils decreased, hemoglobin decreased, lymphocytes decreased, AST increased, gamma-glutamyl transferase increased, ALT increased, creatinine increased, platelets decreased, and glucose serum decreased.**

References: 1. Mayo Clinic. Long QT syndrome diagnosis & treatment. https://www.mayoclinic.org/diseases-conditions/long-qt-syndrome/diagnosis-treatment/drc-20352524. Accessed July 27, 2023. **2.** Vandenberk B et al. *J Am Heart Assoc.* 2016;5(6):e003264. **3.** Kisqali. Prescribing Information. Novartis Pharmaceuticals Corp. **4.** Mayo Clinic. Long QT syndrome symptoms & causes. https://www.mayoclinic.org/diseases-conditions/longqt-syndrome/symptoms-causes/syc-20352518. Accessed July 27, 2023. **5.** Al-Khatib SM et al. JAMA.2003;289(16):2120-2127. **6.** Vered I et al. *J Bone Miner Res.*1990;5(5):469-474.

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