Adding KISQALI, CBC/LFT, and ECG to Breast Cancer Treatment Regimens

iKnowMed℠

Maintaining up-to-date protocols in EHRs is an integral part of providing comprehensive, consistent care. To better support your health care organization, Novartis has developed this iKnowMed 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 modify and use Treatment Regimens and Order Reminders within iKnowMed. This document is not intended to provide any clinical advice or recommendations, which are solely the responsibility of the health care organization. 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.

CBC=complete blood count; LFT=liver function test; ECG=electrocardiogram; EHR=electronic health record.

Indications

KISQALI is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer 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 in postmenopausal women or in men.

IMPORTANT SAFETY INFORMATION

QT interval prolongation. KISQALI has been shown to prolong the QT interval in a concentration-dependent manner. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction, or discontinuation. Across KISQALI treatment groups, 15 of 1054 patients (1.4%) had >500 ms postbaseline QTcF value, and 61 of 1054 (6%) had a >60 ms increase from baseline in QTcF intervals. These electrocardiogram (ECG) changes were reversible with dose interruption and most occurred within the first 4 weeks of treatment. No cases of torsades de pointes were reported.
In MONALEESA-2, on 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.

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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)

QT interval prolongation (continued). Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values <450 ms. Repeat ECG at approximately Day 14 of the first cycle, at the beginning of the second cycle, and as clinically indicated. Monitor serum electrolytes (including potassium, calcium, phosphorus, and magnesium) prior to the initiation of treatment, at the beginning of each of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting therapy with KISQALI.

Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QT prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias
- electrolyte abnormalities

Avoid using KISQALI with drugs known to prolong the QT interval and/or strong CYP3A inhibitors, as this may lead to prolongation of the QTcF interval.

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Upfront ECG Monitoring (continued)[3]

ECG Monitoring		
Baseline		✓
Cycle 1	Day 14	✓
Cycle 2	Day 1	✓ (final scheduled)

- 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 3 ECGs are required—and all are completed within the first 30 days of treatment.

IMPORTANT SAFETY INFORMATION (continued)

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.

Across clinical trials in patients with advanced or metastatic breast cancer treated with KISQALI in combination with an aromatase inhibitor or fulvestrant ("KISQALI treatment groups"), 1.6% of patients treated with KISQALI 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 been observed in the postmarketing setting, with fatalities reported.

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 treatment with KISQALI immediately and evaluate the patient. Permanently discontinue treatment with KISQALI in patients with recurrent symptomatic or severe ILD/pneumonitis.

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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)

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. Consultation with a dermatologist is recommended.

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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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 3 ECGs are required**—and all are completed within the **first 30 days of treatment**.

IMPORTANT SAFETY INFORMATION (continued)

Increased QT prolongation with concomitant use of tamoxifen. KISQALI is not indicated for concomitant use with tamoxifen. In MONALEESA-7, the observed mean QTcF increase from baseline was ≥10 ms higher in the tamoxifen + placebo subgroup compared with the non-steroidal 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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Dosing[3]

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

Recommended starting dose

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

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]. East Hanover, NJ: Novartis Pharmaceuticals Corp. **4.** Mayo Clinic. Long QT syndrome symptoms & causes. https://www.mayoclinic.org/diseases-conditions/long-qt-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.

IMPORTANT SAFETY INFORMATION (continued)

Hepatobiliary toxicity. Across KISQALI treatment groups, increases in transaminases were observed. Across all trials, grade 3/4 increases in alanine aminotransferase (ALT) (11% vs 2.1%) and aspartate aminotransferase (AST) (8% vs 2%) were reported in the KISQALI and placebo arms, respectively.

Among the patients who had grade ≥3 ALT/AST elevation, the median time to onset was 92 days and median time to resolution to grade ≤2 was 21 days for the KISQALI treatment groups.

In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST greater than 3 times the upper limit of normal (ULN) and total bilirubin greater than 2 times the ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 6 (1%) patients and all patients recovered after discontinuation of KISQALI. No cases occurred in MONALEESA-7.

Perform liver function tests (LFTs) before initiating therapy with 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. Recommendations for patients who have elevated AST/ALT grade ≥3 at baseline have not been established.

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EHR Build Guide: Creating a Treatment Regimen for KISQALI

iKnowMed enables the practice to build Treatment Regimens based on groups of orders for easier selection.

Adding KISQALI to an existing Treatment Regimen

iKnowMed uses foundational Treatment Regimens from an embedded clinical decision support tool, Clear Value Plus℠. The Clear Value Plus content is based on National Comprehensive Cancer Network® (NCCN) and NCCN Guidelines.®

Selected Clear Value Plus Treatment Regimens can be modified for patients based on individual patient condition and provider preference.

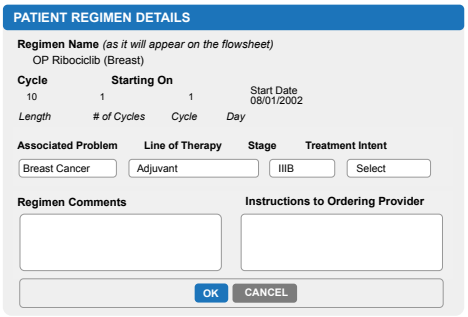
Requests for new or updated regimens can be submitted to Clear Value Plus.

As new tests, treatments, and protocols evolve, it may be appropriate to adjust patients' existing Treatment Regimen and monitoring. With appropriate permissions, users can create Order Sets and Order Panels for ease in adding orders to existing Treatment Regimen flow sheets: Oncology Treatment, Labs Prior to Therapy Initiation, Labs for Ongoing Monitoring

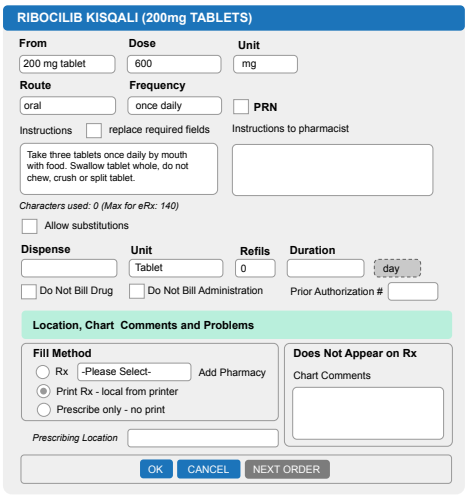
NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Modifying an Existing Treatment Regimen

1. From within a patient chart, select the **Orders, Regimens** tab
2. Select **Search for Regimens**
3. Choose the **Regimen Type (Oncology Treatment)**
4. In the **Filter Oncology Treatments** by search enter **Ribociclib**, then select **Apply**
5. Appropriate **Treatment Options** display
6. Click Select to open **Patient Regimen Details** window
7. Confirm or adjust **Cycle** and **Starting On** values, and other details as desired.
8. Select **OK**
9. In the summary Prescription screen, update details as appropriate, select **OK**
10. Select **OK** to view the order in the patient chart Orders, Regimens tab
11. Select **Review/Save** to add the pending prescription order to the patient Flowsheet on the appropriate cycle/days



Hypothetical example of Patient Regimen Details



Hypothetical example of the Prescription Details for the new order

Note: Prescriptions cannot be ordered prior to the cycle start date. These pending orders are designated with an Rx symbol to indicate its need to be generated on that date.

IMPORTANT SAFETY INFORMATION (continued)

Neutropenia. Across KISQALI treatment groups neutropenia was the most frequently reported adverse reaction (AR) (75%), and a grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 62% of patients in the KISQALI treatment groups. Among the patients who had grade 2, 3, or 4 neutropenia, the median time to grade ≥2 was 17 days. The median time to resolution of grade ≥3 (to normalization or grade <3) was 12 days in the KISQALI treatment groups. Febrile neutropenia was reported in 1.7% of patients in the KISQALI treatment groups. Treatment discontinuation due to neutropenia was 1%.

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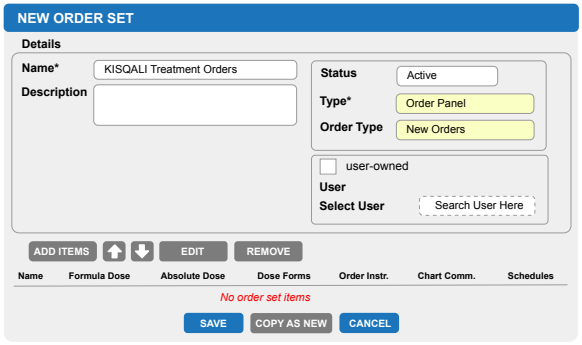
EHR Build Guide: Creating a Treatment Regimen for KISQALI (continued)

Creating an Order Panel

iKnowMed enables the practice to build Order Sets and Order Panels based on groups of orders for easier selection. These orders can be added to a patient's treatment plan and will display on the patient flow sheet. Order Panels can be used to group orders which, are generally selected one at a time.

Step 1: Create an Order Panel for KISQALI Treatment-Associated Orders

1. From the **Manage** menu, select **Order Sets**
2. Select the **Add Order Set** button
3. Name the **Order Set**, for example **KISQALI Treatment Orders**
4. Add a description as desired
5. From the **Type** dropdown, choose **Order Panel**
6. From the **Order Type** dropdown, choose **New Orders**
7. Select **Save** to create the Order Panel and return to the Order Sets list



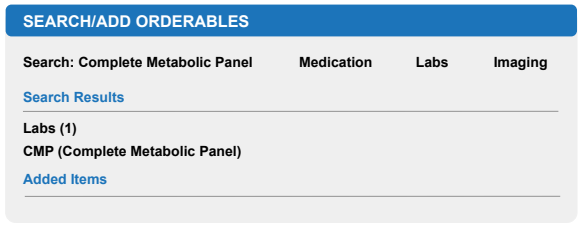
Hypothetical example of creating an Order Panel

Step 2: Add Orders to the Order Panel

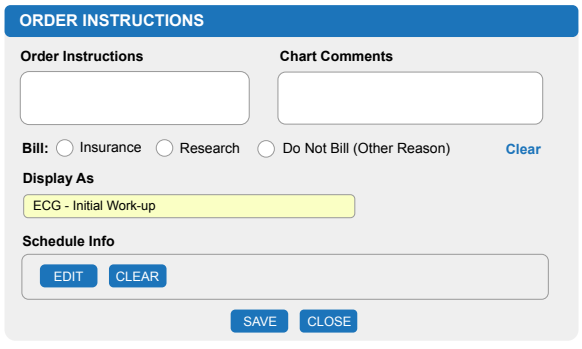
1. To add orders to the new Order Panel, in the Filter Criteria **Name** field, enter the name of the newly created Order Panel
2. Select the **Order Panel** to add items
3. In the **Order Set Details** window, select **Add Items**
4. The **Search/Add Items** window is displayed; check the **Labs** category, search for and select the **CMP**
5. Then check the procedures category, search for ECG and select
6. Select the item to add to the Order Set, then select **Edit** to add **Display Name** and any desired instructions
7. In **Display As**, enter a descriptive name, for example **ECG– Initial Work-up**
8. In **Schedule Info** section, select **Edit**

Note: Adding schedule information allows the item to display properly when added to the flow sheet.

9. Define time frames, for example **"Today"** or **"Within 1 Week"**, then select OK
10. Select **Save** to complete the item



Hypothetical example of Search / Add Orderables



Hypothetical example of adding a Display as Name and Order instruction options

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 Treatment Regimen for KISQALI (continued)

Step 3: Add Labs To Be Done Prior To Therapy Initiation

1. Within the Order Panel, from Search/Add Orderables, select the **Labs** category
2. Search for and select **CMP** (complete metabolic panel)
3. Then select **Edit** to add appropriate descriptive Display Name, such as Pre-therapy CBC, CMP, and ECG
4. Under the Schedule Info heading select **Edit** to add appropriate time frames
5. Select **OK**, then select **Save**

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. In animal reproduction studies, administration of KISQALI to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve. 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: Implementing Order Reminders in iKnowMed

For cancer centers that would like to implement Order Reminders for their patients taking KISQALI, the following information outlines how to create an Order Reminder of requirements when a patient is prescribed KISQALI. The guide uses logic to determine if a patient needs additional testing.

This guide will walk through the creation of an Order Reminder for patients for whom KISQALI has been ordered. The following example alert is designed to prompt clinicians to the risk of QT interval prolongation for patients being treated with KISQALI. KISQALI has been shown to prolong the QT interval in a concentration-dependent manner. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction, or discontinuation. Across KISQALI treatment groups, 15 of 1054 patients (1.4%) had >500 ms postbaseline QTcF value, and 61 of 1054 (6%) had a >60 ms increase from baseline in QTcF intervals. These electrocardiogram (ECG) changes were reversible with dose interruption and most occurred within the first 4 weeks of treatment. No cases of torsades de pointes were reported. In MONALEESA-2, on 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.[3]

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values <450 ms. Repeat ECG at approximately Day 14 of the first cycle, at the beginning of the second cycle, and as clinically indicated. Monitor serum electrolytes (including potassium, calcium, phosphorus, and magnesium) prior to the initiation of treatment, at the beginning of each of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting therapy with KISQALI.[3]

Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QT prolongation, including patients with:[3]

- Long QT syndrome
- Uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias
- Electrolyte abnormalities

Avoid using KISQALI with drugs known to prolong the QT interval and/or strong CYP3A inhibitors, as this may lead to prolongation of the QTcF interval.[3]

Creating Reminders With Order Reminder Rules

1. Navigate to Admin, **Practice Preferences**
2. In the Order Reminder Settings section, select **Add Rule**
3. Select appropriate problem
4. Select the Order Type and the Select order
5. Choose to display the reminder when the order is Present in the chart
6. Enter desired Reminder Text
7. Select **Save**
8. When the information in the chart meets the rule criteria, the Chart Alert icon displays next to the Associated Problem. Clicking the icon displays the Reminder Text.

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
- The instructions have not been designed to meet and are not tools and/or solutions for meeting Meaningful Use, Advancing Care Information, and/or any other quality/accreditation requirement
-

For more information on how the Novartis HIT Team can collaborate with your organization to identify shared priorities please email: HIT.Novartis@novartis.com

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, creatinin 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]. East Hanover, NJ: 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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