Direct Health Care Professionals Communication (DHPC)

Subject: Important information regarding nitrosamine impurity levels related to investigational use of ribociclib in early breast cancer

Dear Health Care Professional,

The purpose of this letter is to share important information regarding nitrosamine impurity levels related to use of ribociclib in early breast cancer (eBC). We recently provided this information to investigators involved in ribociclib eBC clinical trials, and are sharing this information with all oncology health care providers. Please note, KISQALI® (ribociclib) is not labeled for use in eBC.

Importantly, there is no impact of this communication on patient use of KISQALI® (ribociclib) 200 mg tablets in its approved indication of metastatic breast cancer.

The FDA and other global regulatory authorities regularly evaluate acceptable levels of nitrosamine impurities in medications. Acceptable daily intake limits for nitrosamines in medications are set by regulators to levels that approximate to a cancer risk of one additional case in 100,000 people based on a conservative assumption of daily exposure to the impurity over a lifetime (70 years). In August 2023, FDA issued a guidance document entitled "Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs)," which provides drug manufacturers and applicants with a recommended framework for a risk-based safety assessment. Ribociclib contains a nitrosamine impurity at a level which currently **exceeds** the acceptable intake limits recently recommended by FDA and other global health authorities for eBC and other early cancers. Results from a new preclinical study conducted in mice showed that the nitrosamine impurity was mutagenic at all dose levels. This means that exposure to this impurity could potentially increase the risk of developing a secondary malignancy. The extent of this risk relative to the approximations above remains unknown.

Novartis is in the process of implementing manufacturing adjustments for ribociclib to ensure alignment with the latest regulatory standards on intake limits for nitrosamines in medications in eBC.

KISQALI® (ribociclib) is currently approved by regulatory authorities and launched for the treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (locally) advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant. Again, there is no impact on patient use of KISQALI® (ribociclib) in its approved indication.

For additional information, please contact Novartis US Medical Affairs – Medical Information.

Email: mic.inquiry@novartis.com

Patient Language Summary—Intended for Health Care Professional use only.

Direct Health Care Professionals Communication (DHPC) Attachment – Patient Language Summary

Trace amounts of a type of impurity called 'nitrosamines' can be found in water and foods, including cured and grilled meats, dairy products, and vegetables. Nitrosamine impurities may increase the risk of cancer if people are exposed to them above acceptable levels.

The FDA and other global regulatory authorities have been investigating the presence of nitrosamines in medications. In 2023, FDA issued a guidance document entitled "Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs)," which defines the acceptable levels of nitrosamines for drug manufacturers. A person taking a drug that contains nitrosamines at-or-below the acceptable daily intake limits every day for 70 years is not expected to have an increased risk of cancer (additive risk of 1 in 100,000).

We recently shared with investigators involved in ribociclib early breast cancer clinical trials that ribociclib contains a nitrosamine impurity at a level which currently **exceeds** the acceptable intake limits recently recommended by FDA and other global health authorities for early breast cancer and other early cancers. Importantly, this does not impact patient use or commercial supply of KISQALI® (ribociclib) in its approved indication of advanced or metastatic breast cancer.

A recent study performed in mice showed that the nitrosamine impurity in ribociclib is mutagenic. This means that exposure to this impurity could potentially increase the risk of developing another type of cancer in the future. At this time, the exact chances of whether this will occur is not known.

Novartis is currently in the process of implementing manufacturing adjustments for ribociclib to ensure alignment with the latest regulatory standards in early breast cancer. Again, this does not affect use in advanced or metastatic breast cancer, and patients with advanced or metastatic breast cancer should continue taking their medication. Please note, ribociclib is not labeled for use for early breast cancer.

In conclusion, nitrosamines in medications are an issue that regulatory agencies, pharmaceutical companies, and health care providers are actively addressing. By staying informed, following recommendations from health care professionals, and participating in open communication with your health care team, you can make informed decisions about your medication use and overall health.

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