29 October 2024

IMPORTANT DRUG WARNING

Subject: **Gavreto® (pralsetinib), New Warning and Precaution: Severe and Fatal Infection**

Dear Health Care Provider,

The purpose of this letter is to inform you of important safety information for Gavreto. Gavreto is a kinase inhibitor approved for treatment of adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer as detected by an FDA approved test (NSCLC).

Background on the safety concern

Pralsetinib is indicated for the treatment of adult patients with RET fusion-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC), as well as adult and pediatric patients 12 years of age and older with advanced or metastatic RET- fusion-positive thyroid cancer who require systemic therapy.

In the ongoing phase III trial AcceleRET-Lung (BO42864, NCT04222972)[1], being conducted by Hoffmann-La Roche , a randomized, open label study of pralsetinib versus standard of care (SOC) in first-line treatment of RET fusion- positive, metastatic non-small cell lung cancer (NSCLC) patients, an ad hoc analysis has demonstrated an imbalance regarding the risk of severe and fatal infection, including severe opportunistic infections, between the pralsetinib and SOC arms. The ad hoc analysis was triggered by an observation of an imbalance in fatal adverse events between the two treatment arms, primarily due to infections. Fatal adverse events were reported in 14 patients (13.0%) in the pralsetinib arm, versus 5 patients (4.8%) in the SOC arm. Of these fatal events, fatal infection events occurred in 5 patients (4.6%) in the pralsetinib arm, and none in the SOC arm. Non-infection fatal AEs in the pralsetinib arm did not reveal any particular pattern.

At the time of the ad hoc review, 212 patients had received at least any amount of any study treatment, 108 patients in the pralsetinib arm, and 104 patients in the SOC arm. Severe (grade 3-5) infection events occurred in 28 (25.9%) pralsetinib treated patients versus 8 (7.7%) patients receiving SOC. Statistical analysis performed on severe infection adverse events demonstrate a significant imbalance, with Fisher's exact two-tailed p-value of 0.0004. The risk ratio, calculated using the Aalen-Johanssen estimator[2] taking into account

variable time on treatment and competing events, indicated a significantly higher risk of severe infection with pralsetinib vs SOC treatment (risk ratio 3.33; 95% CI: [1.57, 7.06], with the lower limit of the 95% CI > 1). Half of the severe infections in pralsetinib treated patients occurred within the first 66 days of treatment. Approximately half of the severe infections were lung infections. Most severe infections were not preceded by neutropenia or lymphopenia. Fatal infections occurred in 5 (4.6%) patients in the pralsetinib arm, and in 0 patients in the SOC arm. Severe opportunistic infections, including pneumocystis jirovecii pneumonia, cytomegalovirus pneumonia, legionella pneumonia and esophageal candidiasis occurred in 7 (6.5%) of pralsetinib treated patients, and in 0 patients receiving SOC.

This data supports concluding that severe infections, including opportunistic infections, warrants an update to the Product Information in Warnings and Precautions, to alert prescribers and patients of this risk.

The corresponding updates to the product label will be forthcoming.

Prescriber Action

Monitor patients closely for signs and symptoms of infection, and treat appropriately according to local/institutional guidelines. Ensure patients are up to date on vaccinations according to local/institutional guidelines.

Withhold Gavreto in the presence of active infection, and resume with dose reduction following labeled prescribing information when infection resolves. Permanently discontinue Gavreto in the setting of life-threatening infection.

Reporting Adverse Events

Health care providers and patients are encouraged to report adverse events in patients taking Gavreto to Rigel Pharmaceuticals, Inc. at 1-800-983-1329 or producthelp@rigel.com. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Company Contact Point

You may also contact our medical information department at 1-800-983-1329 if you have any questions about the information contained in this letter or the safe and effective use of Gavreto.

This letter is not intended as a complete description of the benefits and risks related to the use of Gavreto. Please refer to the enclosed full prescribing information and medication guide.

Sincerely,

Lisa Rojkjaer

Lisa Rojkjaer, MD

Executive Vice President, Chief Medical Officer

Enclosure(s): Gavreto (pralsetinib) Full Prescribing Information/Medication Guide

References:

1. https://clinicaltrials.gov/search?intr=NCT04222972
2. Stegherr et al. Trials. 2021 Jun 29;22(1):420. doi: 10.1186/s13063-021-05354-x. PMID: 34187527; PMCID: PMC8244188

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