<Date>

GAVRETO (pralsetinib): Increased risk for tuberculosis and measures to minimise this risk

Dear Healthcare professional,

Hoffmann-La Roche in agreement with <the European Medicines Agency> and the <National Competent Authority > would like to inform you of the following:

Summary

- **Tuberculosis, mostly extrapulmonary, has been reported in patients receiving pralsetinib.**
- **Before starting treatment, patients should be evaluated for active and inactive ("latent") tuberculosis, as per local recommendations.**
- **In patients with active or latent tuberculosis, standard antimycobacterial therapy should be initiated before treatment with Gavreto is started.**

Background on the safety concern

In the European Union, Gavreto is indicated as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor.

An investigation of global safety data for Gavreto identified 9 cases of tuberculosis in pralsetinib treated patients, of which the majority (7/9) occurred in tuberculosis-endemic regions. The events occurred in patients with and without prior known history of tuberculosis. In most cases, extrapulmonary tuberculosis was reported such as lymph node tuberculosis, peritoneal tuberculosis, or renal tuberculosis.

Among patients treated in the ARROW trial (N=528), tuberculosis of any severity was reported in 4 (0.8%) patients, and a grade 3-4 event was reported in one patient (0.2%). This corresponds to a frequency of uncommon for tuberculosis (≥ 1/1,000 to < 1/100).

Before starting treatment, patients should be evaluated for active and inactive ("latent") tuberculosis, as per local recommendations. In patients with active or latent tuberculosis, standard antimycobacterial therapy should be initiated before treatment with Gavreto is started.

Co-administration of pralsetinib with strong CYP3A4 inducers such as rifabutin, rifampicin can decrease pralsetinib plasma concentrations, which may decrease the efficacy of pralsetinib. Co-administration of pralsetinib with strong CYP3A4 inducers should be avoided. If co-administration cannot be avoided, increase the pralsetinib dose.

An update to the product information to include the risk of tuberculosis and recommendations for testing and treatment is ongoing.

Lee YP, Jeong BH, Eun Y, et al. Extrapulmonary tuberculosis in patients with RET fusion-positive non-small cell lung cancer treated with pralsetinib: A Korean single-centre compassionate use experience. *Eur J Cancer*. 2021;159:167-173. doi:10.1016/j.ejca.2021.09.037

Call for reporting

Healthcare professionals should report any adverse events suspected to be associated with Gavreto (pralsetinib) in accordance with the national spontaneous reporting system <include the details (e.g., name, postal address, fax number, website address) on how to access the national spontaneous reporting system>

Company contact point

Should you have any questions regarding the use of Gavreto (pralstetinib), please feel free to contact us at: [Insert local contact information e.g. Genentech Medical Information/Communications Department at (800) 821-8590].

Yours sincerely,

<Company Name of Affiliate>

<Signature of authorised contact person>

Zoe Conway, MB BS
Global Head – Portfolio Clinical Safety (PCS)

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	GAVRETO (pralsetinib)
Marketing authorisation holder(s)	F. Hoffman-La Roche, Ltd.
Safety concern and purpose of the communication	To inform healthcare professionals on the increased risk for tuberculosis and measures to minimise this risk
DHPC recipients	Oncologists The target group would be further defined at national level, in agreement with the respective national competent authority.
Member States where the DHPC will be distributed	All EEA member states where Gavreto is authorised.
Timetable	**Date**
DHPC and communication plan (in English) agreed by PRAC	12 May 2023
DHPC and communication plan (in English) agreed by CHMP	25 May 2023
Submission of translated DHPCs to the national competent authorities for review	01 Jun 2023
Agreement of translations by national competent authorities	08 Jun 2023
Dissemination of DHPC	16 Jun 2023