Direct Healthcare Professional Communication

Esbriet (pirfenidone): Important safety update and new recommendations to prevent Drug-Induced Liver Injury (DILI)

Dear Healthcare Professional,

F. Hoffmann-La Roche Ltd. [or local Affiliate Name] in agreement with <the European Medicines Agency> and the <National Competent Authority> would like to inform you of the following:

Summary

- **Severe cases of drug-induced liver injury (DILI) with Esbriet (pirfenidone), including cases with fatal outcome have recently been reported.**
- **Liver function tests (ALT, AST, bilirubin) should be performed before starting treatment with Esbriet (pirfenidone), subsequently every month for the first 6 months and then every 3 months for the duration of treatment.**
- **Prompt clinical evaluation and liver function tests should be performed in patients with symptoms indicating drug-induced liver injury, such as fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.**
- **Elevated transaminases may require dose reduction, interruption or permanent discontinuation of Esbriet (pirfenidone). In the event of significant elevation of liver aminotransferases with hyperbilirubinaemia or clinical signs and symptoms of drug-induced liver injury, the dose of Esbriet (pirfenidone) should be permanently discontinued.**

Background on the safety concern

Esbriet (pirfenidone) is an anti-fibrotic and anti-inflammatory medicine indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

Recently, serious hepatic adverse events including isolated cases with fatal outcome have been reported in IPF patients treated with pirfenidone. Although the aetiology is unclear, idiosyncratic reactions may underlie DILI following treatment with pirfenidone. During clinical development, an increased cumulative incidence of hepatic treatment-emergent adverse events was observed in patients treated with pirfenidone (9.5%) vs. placebo (4.3%), the majority of which were laboratory abnormalities.

An overview of the available data from clinical trials, post-marketing data and literature showed that the majority of the reported hepatic events occurred within the first months of treatment with pirfenidone. Therefore, hepatic transaminases and bilirubin levels should be investigated before treatment initiation, subsequently at monthly intervals for the first 6 months and then every 3 months thereafter. In addition, prompt clinical evaluation and liver function testing should be performed in patients with symptoms that may indicate drug-

induced liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

In the event of significant elevation of liver aminotransferases or clinical signs and symptoms of liver injury, the dose of Esbriet should be adjusted or treatment permanently discontinued according to the guidelines in the summary of product characteristics. If a patient exhibits aminotransferase elevation >3 to <5 x ULN accompanied by hyperbilirubinaemia or clinical signs or symptoms indicative of liver injury, or aminotransferase elevation to ≥5 x ULN, Esbriet should be permanently discontinued.

The summary of the product characteristics will be updated in line with this new safety information.

Please also refer to the updated safety checklist for prescribing physicians, which is enclosed. Additional copies are available through your local contact point.

Call for reporting

Healthcare professionals should report any adverse events suspected to be associated with the use of Esbriet according to national reporting requirements.

<Affiliate to please include name, postal address, fax number, website address of the national spontaneous reporting system>

Company contact point

< Affiliate to please include contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

Yours sincerely,

<Company Name of Affiliate>

<Signature of authorised contact person>

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	**Esbriet® (pirfenidone)**
Marketing authorisation holder(s)	Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany
Safety concern and purpose of the communication	Important safety update and new recommendations to prevent drug-induced liver injury.
DHPC recipients	Healthcare professionals who may prescribe or dispense pirfenidone (all respiratory physicians, hospital pharmacists) and healthcare professionals (hepatologists) who may examine patients with developing liver injury whilst receiving pirfenidone. *[details to be confirmed, upon discussions with national competent authorities (NCAs) in countries where the product is currently being marketed].*
Member States where the DHPC will be distributed	All EU-Member States.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	29 September 2020
DHPC and communication plan (in English) agreed by CHMP/CMDh	1 October 2020
Submission of translated DHPCs to the national competent authorities for review	8 October 2020
Agreement of translations by national competent authorities	15 October 2020
Dissemination of DHPC	29 October 2020