29th October 2020

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

Dear Healthcare Professional,

Roche Products (Ireland) Limited in agreement with the European Medicines Agency and the Malta Medicines Authority (MMA) 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-

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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 to: the Drug Surveillance Centre in Roche Products (Ireland) Limited by telephone (01-4690700) or email (Ireland.drug_surveillance_centre@roche.com).

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form available online at http://www.medicinesauthority.gov.mt/adrportal and sent to Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN or sent by email to: postlicensing.medicinesauthority@gov.mt.

Company contact point

Should you have any questions regarding the use of Esbriet (pirfenidone) please feel free to contact Medical Information at Roche Products (Ireland) Limited by telephone (01 4690700), fax (01 4690791) or email (Ireland.druginfo@roche.com).

Yours sincerely,

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Signer Name: James Mawby
Signing Reason: I approve this document
Signing Time: 16-Oct-2020 | 12:39:41 PM CEST
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