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

Dear Healthcare Professional,

Roche Products Limited in agreement with the European Medicines Agency (EMA) and the Medicines and Healthcare Regulatory Agency (MHRA) would like to inform you of the following:

Summary

- Severe cases of drug-induced liver injury (DILI), including cases with fatal outcome, have recently been reported in patients treated with Esbriet (pirfenidone).
- Liver function tests (ALT, AST, bilirubin) should be performed before starting treatment with Esbriet (pirfenidone), 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 (SPC) 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 from the electronic Medicines Compendium (eMC) at www.medicines.org.uk.

Call for reporting

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or calling +44 (0)1707 367554.
This educational material is provided by Roche Products Limited and is mandatory as a condition of the Marketing Authorisation in order to further minimise important selected risks.

Company contact point

Should you have any questions about the information in this letter or require any further assistance, please contact Roche Medical Information by phone on +44(0)800 328 1629 or via e-mail medinfo.uk@roche.com

Yours sincerely,

Roche Products Limited

Dr Marius Scholtz
Chief Medical Officer