08-Dec-19

Roche

Important Safety Update on ESBRIET® (pirfenidone) and Drug-Induced Liver Injury (DILI)

Dear Healthcare professional,

Roche Products Saudi Arabia in agreement with Saudi Food and Drug Authority would like to inform you of the following:

Summary

- **Current Prescribing Information:**
  - Elevations of liver enzymes > 3 x upper limit of normal, rarely associated with concomitant increases in bilirubin, are known risks of Esbriet® and are thus described in the Warning & Precaution and Undesirable Effects section of the Prescribing Information.
- **New safety information:**
  - Clinical manifestations of DILI including cases with fatal outcome– possibly caused by idiosyncratic reactions to pirfenidone – have recently been reported in individual patients. Based on these findings, the Prescribing Information will be updated to adequately describe the risk of clinically relevant DILI and recommend additional monitoring of the liver function in the presence of clinical signs or symptoms suggestive of liver injury.

Background on the safety concern

Pirfenidone (5-methyl-1-phenyl-2-1[H]-pyridone) is an anti-fibrotic and anti-inflammatory agent indicated for the treatment of Idiopathic Pulmonary Fibrosis (IPF).

No evidence of liver damage following exposure to pirfenidone was observed during toxicology studies. During clinical development, an increased cumulative incidence of hepatic treatment-emergent adverse events was reported in patients treated with pirfenidone (9.5%) vs. placebo (4.3%). The majority of these events were clinically silent laboratory abnormalities without consequences. Based on these data, elevations of liver enzymes, rarely associated with bilirubin increases, are described in the relevant sections of the Prescribing Information along with the recommendation to monitor liver enzymes during treatment and reduce the dosage or discontinue treatment as required.

Recently, serious hepatic adverse events including isolated cases with fatal outcome have been reported post-marketing in IPF patients treated with pirfenidone. No alternative etiologies or confounding factors could be found in these reports, which were therefore deemed clinically relevant cases of DILI. In the absence of a plausible pharmacodynamics mechanism, these cases appear possibly triggered by idiosyncratic reactions to pirfenidone.
The frequency of clinically relevant DILI detected post-marketing is estimated as rare (≥1/10,000 to <1/1,000).

The majority of the reported hepatic events occurred within the first months of treatment. Therefore, hepatic transaminase and bilirubin levels should be

investigated before treatment initiation and subsequently at monthly intervals for the first 6 months and then every 3 months thereafter. In addition, liver function tests should be promptly measured in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

The benefit-risk profile of Esbriet® in the approved indication remains favourable based on the cumulative analysis of available global clinical and post-marketing safety data. However,
Roche Products Saudi Arabia is working closely with Saudi Food and Drug Authority to update the Prescribing Information in line with the above new safety information.

Call for reporting

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

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Yours sincerely,

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08-Dec-19

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