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(IN REPLY PLEASE QUOTE THIS FILE REF.)

Dear Healthcare Professionals,

Eltrombopag (Revolade): reports of interference with bilirubin and creatinine test results

Your attention is drawn to the Medicines and Healthcare products Regulatory Agency's (MHRA) announcement that there are reports of interference with bilirubin and creatinine test results associated with eltrombopag.

An EU review of data considered the available evidence of laboratory test interference (i.e., bilirubin and creatinine) associated with eltrombopag. Up to 30 Sep 2017, the licence holder of Revolade received 9 reports worldwide of serum discolouration and interference with bilirubin and creatinine test values. Six reports were of suspected interactions with bilirubin test values, of which 2 reported falsely low/normal bilirubin values (false-negative) despite clinically noticeable jaundice. Daily doses of eltrombopag were reported to be 75 mg in 4 cases, 150 mg in 1 case, and 300 mg in 1 case. Three reports were of suspected interactions with creatinine test values leading to falsely high/normal values (false-positive). All 3 cases of a positive interaction with serum creatinine values were in patients with paediatric severe aplastic anaemia on high doses of eltrombopag (to 5 mg/kg and 7.5 mg/kg per day; equivalent to 375 mg).

Of the 9 reported cases of interference, 2 resulted in eltrombopag dose reductions and 2 led to temporarily discontinuation of the medicine. In 1 case eltrombopag was discontinued 4 days after suspected interference with a biological test due to lack of response. Two cases did not result in eltrombopag dose reductions and the action taken with eltrombopag was not reported in the remaining 2 cases.

In addition, several publications describe potential negative interference from eltrombopag on bilirubin testing and positive interference on creatinine test values. Two publications report that eltrombopag did not interfere with aminotransferases and blood urea testing findings.

The mechanism for the eltrombopag interference with bilirubin and creatinine test values appears to be pH-dependent and method- or reagent-specific and related to the colour of eltrombopag in serum. The false-positive interference with creatinine may result in a misleading clinical picture of apparent renal deterioration. The interference with bilirubin is less likely to have clinically significant consequences since the stopping criteria for hepatic disorders are based on rises in serum alanine aminotransferase (ALT) levels and clinical symptoms/evidence of hepatic decompensation, rather than bilirubin values alone.

Healthcare professionals are advised:

- Eltrombopag is highly coloured (reddish-brown) and can cause serum discolouration and interference with the test results of creatinine and bilirubin.
- Be aware that interference with bilirubin (falsely low/normal results) and creatinine (falsely high/normal results) may occur in patients taking eltrombopag.
- If bilirubin and/or creatinine laboratory results are inconsistent with clinical observations, request re-testing using another method to determine the validity of the result.
- The laboratory may consider susceptibility to serum discolouration and other factors that may be relevant when selecting an alternative test method.
- Report suspected adverse drug reactions, including any harm that occurs from a medicine interfering with laboratory test results, to the Yellow Card Scheme.

Please refer to the following website in MHRA for details:
https://www.gov.uk/drug-safety-update/eltrombopag-revolade-reports-of-interference-with-bilirubin-and-creatinine-test-results

In Hong Kong, there are 4 registered pharmaceutical products containing eltrombopag, namely Revolade Tab 25mg (HK-60349), Revolade Tab 50mg (HK-60350), Revolade Tablets 25mg (Spain) (HK-62055) and Revolade Tablets 50mg (Spain) (HK-62056). All products are registered by Novartis Pharmaceuticals (HK) Limited, and are prescription-only medicines. So far, the Department of Health (DH) has received 10 cases of adverse drug reaction related to eltrombopag, but these cases are not related to interference with bilirubin and creatinine test results. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Pharmacovigilance Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

(Joseph LEE)
for Assistant Director (Drug)