A. DHPC Letter and DHPC communication plan

22/02/2022

Xagrid (anagrelide hydrochloride): Risk of thrombosis including cerebral infarction upon abrupt treatment discontinuation

Ref: EMEA/H/C/000480

Dear Healthcare Professional,

Shire Pharmaceuticals Ireland Limited (a subsidiary of Takeda Pharmaceuticals Company Limited) in agreement with the European Medicines Agency (EMA) and <national competent authority> would like to inform you the following:

Summary

- **There is an increased risk of thrombotic complications, including cerebral infarction, upon abrupt anagrelide discontinuation.**
- **Abrupt treatment discontinuation should be avoided due to the risk of sudden increase in platelet counts and potentially fatal thrombotic complications, such as cerebral infarction.**
- **In the event of dosage interruption or treatment withdrawal, monitor platelet counts frequently (refer to SmPC Section 4.4).**
- **Advise patients how to recognize early signs and symptoms suggestive of thrombotic complications, such as cerebral infarction, and if symptoms occur to seek medical assistance.**

Background on the safety concern

Xagrid (anagrelide) is indicated for the reduction of elevated platelet counts in at risk patients with essential thrombocythemia who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy.

A cumulative analysis of company safety database till 6 August 2021 showed 15 events of thrombotic complications, including cerebral infarction, after a recent discontinuation of anagrelide. It was concluded that cerebral infarction, along with other thrombotic complications, while being part of the pre-existing condition/indication, may also occur upon abrupt anagrelide discontinuation, inadequate dosing, or lack of effect.

The mechanism of cerebral infarction following abrupt treatment discontinuation is related to the rebound in platelet count. Platelet count typically will start to rise within 4 days after discontinuation and return to baseline levels in one to two weeks, possibly rebounding above baseline values.

Based upon the available information, the safety information under Section 4.4 "Special Warnings and Precautions for Use" and section 4.8 "Undesirable Effects of Summary of Product Characteristics (SmPC) will be updated to reflect the latest data and recommendations.

Call for reporting
Please report any adverse events experienced by your patients taking Xagrid (anagrelide). Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. When reporting, please provide as much information as possible including information about batch details, medical history, any concomitant medication, onset and treatment dates.

Please report suspected adverse reactions with any medicine or vaccine to the <Competent Health Authority (e.g. Website, email, Address, Contact no.) >
Adverse events should also be reported to Takeda:
Takeda products: <Local Contact Number>

Company Contact point
For questions relating to the content of this communication please contact the Takeda Medical
Information Department
Takeda products: <Country Contact Number>

Marketing Authorization Holder

Yours faithfully,

Sumit Munjal	<Update credentials>
Takeda EU QPPV	Country Medical Director