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CONFIDENTIAL

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Dear Healthcare Professional,

Communication on the association of anagrelide hydrochloride (Xagrid® 0.5mg hard capsules) with cardiovascular risk in patients with essential thrombocythaemia (ET), whatever the patient's medical history or medical condition and a reminder that anagrelide is indicated as a second line therapy in at-risk patients.

Summary

Following a review of all cardiac events reported in patients under 50 years of age treated with anagrelide, section 4.4 'Special warnings and precautions for use', cardiovascular section of the Xagrid Summary of Product Characteristics (SmPC) has been re-enforced.

A statement has been added stating that serious cardiovascular adverse events may occur in patients without any suspected heart disease and with normal previous cardiovascular investigations.

The addition of this statement to the Xagrid SmPC does not alter the current benefit/risk of anagrelide in the context of its therapeutic indication as a second line treatment in at risk essential thrombocythaemia (ET) patients.

The communication of this information has been agreed with the European Medicines Agency and the Irish Medicines Board (IMB).

Further information on the safety concern

Recently, as part of ongoing surveillance, Shire conducted a review of all cardiac events reported in patients under 50 years of age treated with anagrelide. Serious cardiovascular adverse events have occurred in these younger patients with no suspected heart disease, normal cardiovascular pre-treatment examinations and controlled myeloproliferative disease. This led to re-enforcing the cardiovascular warning in Section 4.4 'Special precautions and warnings for use' of the EU SmPC.

Also in the same section of the EU SmPC, the list of serious cardiovascular adverse reactions has been expanded to include cardiomyopathy and cardiac arrhythmias, to be consistent with

the tabulated summary of adverse events (Section 4.8). Changes are shown in red and are underlined below.

Special warnings and precautions for use

Cardiovascular

Serious cardiovascular adverse events including cases of cardiomyopathy, cardiomegaly, congestive heart failure and cardiac arrhythmias have been reported (see section 4.8).

Anagrelide should be used with caution in patients of any age with known or suspected heart disease. Moreover, serious cardiovascular adverse events have also occurred in patients without suspected heart disease and with normal pre-treatment cardiovascular examination.

Anagrelide should only be used if the potential benefits of therapy outweigh the potential risks.

Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III and because of its positive inotropic effects, a pre-treatment cardiovascular examination (including further investigation such as echocardiography, electrocardiogram) is recommended. Patients should be monitored during treatment for evidence of cardiovascular effects that may require further cardiovascular examination and investigation.

Further information on recommendations to healthcare professionals

Healthcare Professionals are reminded that patients should be monitored before and during treatment for evidence of cardiovascular effects that may require further cardiovascular examination and investigation. This is in order to detect any possible cardiovascular effects and the institution of appropriate care to patients.

Xagrid is indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia (ET) patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy. An at risk essential thrombocythaemia patient is defined by one or more of the following features:

- >60 years of age or
- a platelet count > 1000 x 10^9/l or
- a history of thrombo-haemorrhagic events.

Call for reporting

Please report any adverse events experienced by your patients taking anagrelide. When reporting, please provide as much information as possible including information about medical history, any concomitant medication, onset and treatment dates.

Adverse events should be reported according to local requirements. Adverse events should be reported to the Pharmacovigilance Unit at the Irish Medicines Board (IMB) (imbpharmacovigilance@imb.ie). Information about adverse event reporting can be found on the IMB website (www.imb.ie).

Adverse events should also be reported to Shire:-

Via e-mail to: GlobalPharmacovigilance@shire.com

Tel number: +44 1256 894000

Fax number: +44 1256 894715

Should you have any questions, please contact the Shire Medical Information Department:

Tel: 1 800 818016. Email: medinfoie@shire.com

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Yours faithfully,

Dr. Birgitt Gellert
Vice President Medical Surveillance and
European Qualified Person for Pharmacovigilance

Dr. David Williams
Medical Director

Enclosures

Text of the revised SmPC(s) with changes highlighted