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13 October 2015

XALKORI▼ (crizotinib) Hard Capsules 200 and 250 mg for oral use
Inclusion of a new warning regarding cardiac failure

Dear Healthcare Professional,

Pfizer in agreement with the European Medicines Agency and the Health Products Regulatory Authority would like to inform you of the following:

Summary

- Severe, sometimes fatal, cases of cardiac failure have been reported in patients with ALK-positive NSCLC treated with crizotinib.
- Cardiac failure occurred in patients with or without pre-existing cardiac disorders, receiving crizotinib.
- Patients should be monitored for signs and symptoms of heart failure (dyspnea, oedema, rapid weight gain).
- If symptoms of cardiac failure are observed, appropriate measures such as dosing interruption, dose reduction, or discontinuation should be considered.

Background information on the safety concern

XALKORI is a medicinal product containing crizotinib. XALKORI is indicated for the treatment of adults with previously treated anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC).
A safety review of crizotinib based on data from clinical trials and reports from clinical practice concluded that there is a risk of cardiac failure following the use of crizotinib.

Across clinical studies in patients with ALK-positive NSCLC (n=1669), a total of 19 (1.1%) patients treated with crizotinib had any grade cardiac failure[1], 8 (0.5%) patients had Grade 3 or 4, and 3 (0.2%) patients had fatal outcome.

In the post marketing experience, as of 25 February 2015, it is estimated that more than 14700 patients have received crizotinib and cardiac failure was reported in 40 patients (reporting rate 0.27%). The majority occurred during the first month of treatment. A fatal outcome was reported for 15 of them. Seven cases have been identified where symptoms

[1] Cardiac failure (Cardiac failure, Cardiac failure congestive, Ejection fraction decreased, Left ventricular failure, Pulmonary oedema).

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of cardiac failure resolved after discontinuation of crizotinib, and in three of these cases symptoms reoccurred when crizotinib was subsequently re-introduced. In 3 out of these 7 cases, no confounding cardiac disorders (past medical history, comorbid conditions, and concurrent medications) were identified.

In order to prevent or minimize the above risk, the text in the Annex has been added to the XALKORI Summary of Product Characteristics (SmPC).

CALL FOR REPORTING

Healthcare professionals are reminded to report any adverse reactions suspected to be associated with the use of XALKORI in accordance with the national spontaneous reporting system.

Suspected adverse reactions should be reported to the HHPRA using a Yellow Card obtained either from the HPRA, or electronically via the website at www.hpra.ie. Adverse reactions can also be reported to the HPRA by calling

(01) 676 4971.

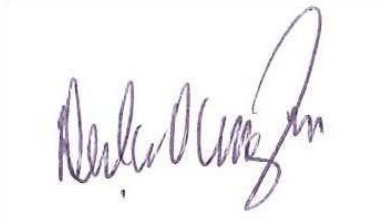
Suspected adverse drug reactions may also be reported to Pfizer Medical Information on 1800 633 363.

Company contact point

For further information or any questions on cardiac failure associated with the use of XALKORI please contact Pfizer Medical Information at Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS or Tel: 1800 633 363 and ask for Medical Information.

▼ XALKORI is subject to additional monitoring, as it contains a new active substance authorised in the EU after 1 January 2011, and is conditionally approved.

Yours sincerely,



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ANNEX: Changes to the SmPC for XALKORI

4.4 Warnings and precautions

Cardiac failure

In clinical studies with crizotinib and during post marketing surveillance, severe, life-threatening, or fatal adverse reactions of cardiac failure were reported (see section 4.8).

Patients with or without pre-existing cardiac disorders, receiving crizotinib, should be monitored for signs and symptoms of heart failure (dyspnoea, oedema, rapid weight gain from fluid retention). Dosing interruption, dose reduction, or discontinuation should be considered as appropriate if such symptoms are observed.

4.8 Undesirable effects

Table 3. *Adverse reactions reported in crizotinib randomised Phase 3 Study 1.*

Cardiac failure[f] (common, 1%)

f. Cardiac failure (Cardiac failure, Cardiac failure congestive, Ejection fraction decreased, Left ventricular failure, Pulmonary oedema). Across clinical studies (n=1669), 19 (1.1%) patients treated with crizotinib had any grade cardiac failure, 8 (0.5%) patients had Grade 3 or 4, and 3 (0.2%) patients had fatal outcome.

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