1 April 2016
EMA/375653/2016
Committee for Medicinal Products for Human Use (CHMP)

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation

Active substance: crizotinib

Procedure no.: EMEA/H/C/PSUSA/00010042/201508

Period covered by the PSUR: 26 February 2015 - 25 August 2015

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for crizotinib, the scientific conclusions of CHMP are as follows:

Following cumulative reviews of a number of adverse events, three adverse events were identified where a causal relationship with crizotinib was supported.

In the review of "Blood testosterone decreased", the preclinical and clinical data supported a causal relation between crizotinib and blood testosterone decreased. Although the large majority of the adverse events of "Blood testosterone decreased" as well as the related symptoms reported with crizotinib were non-serious, cases reporting improvement of symptoms with testosterone replacement have been identified and support a causal relationship with crizotinib. Section 4.8 of the SmPC should be revised to add the AR "Blood testosterone decreased".

In the review of gastrointestinal disorders, 62 cases reporting "Oesophagitis" have been identified. All ARs reported from clinical trial sources and the majority (51.8%) from post-marketing were serious. In addition, 29 cases of "Oesophageal ulcers and perforation", all serious, were also identified. The level of evidence is considered sufficient to support a causal relationship between crizotinib and "Oesophagitis" and "Oesophageal ulcer". Section 4.8 of the SmPC should be revised to add the AR "Oesophagitis".

In the review of Visual effects, 65 cases reporting 77 relevant grade 3/4 and/or serious ARs under the SOC "Eye disorders" were identified. Cases reporting positive dechallenge have been identified as well as cases reporting rapidly worsening visual AE while on crizotinib, leading to vision loss, supporting a causal relationship with crizotinib. Sections 4.2, 4.4 and 4.8 of the SmPC should be revised to reinforce the existing warning and to inform that adverse reactions which may result in vision loss have been reported with crizotinib.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing crizotinib were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation

On the basis of the scientific conclusions for crizotinib the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing crizotinib is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation should be varied.