Direct Healthcare Professional Communication

< XX-XXX-2022>

Xalkori (crizotinib): Vision disorders, including risk of severe visual loss, need for monitoring in paediatric patients

Dear Healthcare Professional,

Pfizer Europe MA EEIG in agreement with the European Medicines Agency and the [national competent authority] would like to inform you of the following:

Summary

- Vision disorders are a known risk with crizotinib and have been reported in 61% of paediatric patients with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) or recurrent, or refractory anaplastic lymphoma kinase (ALK)-positive unresectable inflammatory myofibroblastic tumour (IMT), in crizotinib clinical trials.

- As paediatric patients may not report or notice changes in vision spontaneously, healthcare professionals should inform patients and caregivers of the symptoms of vision disorders and the risk of visual loss, and to contact their healthcare provider if visual symptoms or visual loss develop.

- Paediatric patients should be monitored for vision disorders. A baseline ophthalmologic examination should be undertaken prior to starting crizotinib, with follow-up examinations within 1 month, every 3 months thereafter, and upon observation of new visual symptoms.

- In paediatric patients, a dose reduction should be considered if Grade 2 ocular disorders arise and crizotinib should be permanently discontinued for Grade 3 or 4, unless another cause is identified.

Background information

Xalkori has been authorised since 2012 as a monotherapy in adults for the treatment of patients with ALK-positive advanced non-small cell lung cancer (NSCLC) and in *ROS1*-positive NSCLC since 2016.

In adults, vision disorders have been reported in 1084 of the 1722 (63%) clinical trial patients with ALK-positive or *ROS1*-positive advanced NSCLC treated with Xalkori. Grade 4 vision loss was reported in 4 (0.2%) patients. Optic atrophy and optic nerve disorder have been reported as potential causes of vision loss.

Since MMM/2022, Xalkori is also indicated in paediatric patients (age ≥6 to <18 years) as monotherapy for the treatment of patients with relapsed or refractory systemic ALK-positive ALCL or patients with, recurrent, or refractory ALK-positive unresectable IMT.

In paediatric patients (age ≥6 to <18 years), vision disorders were reported in 25 out of 41 (61%) patients treated with crizotinib for these indications in clinical trials. The most common visual symptoms were blurred vision (24%), visual impairment (20%), photopsia (17%) and vitreous floaters (15%). Of the 25 patients who experienced vision disorders, one patient experienced grade 3 optic nerve disorder.

Vision disorders are more challenging to detect in paediatric patients, as they may not report or notice changes in vision without specific questioning of symptoms and examinations. For these reasons, the following is recommended for paediatric patients with ALK-positive ALCL or ALK-positive IMT:

- Inform patients and caregivers of the symptoms of vision disorders (e.g., perceived flashes of light, blurry vision, light sensitivity, floaters) and potential risk of visual loss.

- Obtain a baseline ophthalmologic examination for young patients with ALCL or IMT prior to starting crizotinib.

- Conduct follow-up ophthalmologic examinations within 1 month of starting crizotinib, every 3 months thereafter, and upon presentation of any new visual symptoms. Ophthalmological evaluation should consist of best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography (OCT) and other evaluations as appropriate.

- Consider a dose reduction of crizotinib for patients who develop Grade 2 ocular disorders.

- Withhold crizotinib pending evaluation for any Grade 3 or 4 ocular disorders, and permanently discontinue crizotinib for Grade 3 or 4 ocular disorders unless another cause is identified.

The product information and the educational material for patients and caregivers have been updated to contain instructions/recommendations in paediatric patients about the risk of vision disorders, including severe vision loss.

Call for reporting

Healthcare professionals should report any adverse events suspected to be associated with the use of Xalkori (crizotinib) via their national reporting system.

[insert local contact]

Company contact point

If you have any questions about this letter or for more information about Xalkori please contact [add national company contact]

if applicable>

Yours sincerely,

<Name>
<Title>

cc

<Name>, <Title>
<Name>, <Title>
<Name>, <Title>

Communication plan for Direct Healthcare professional communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	XALKORI (crizotinib) 200 mg hard capsules XALKORI (crizotinib) 250 mg hard capsules
Marketing authorisation holder(s)	Pfizer Europe MA EEIG
Safety concern and purpose of the communication	Vision disorders (including risk of severe visual loss) and need for monitoring in paediatric patients with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) or, recurrent, or refractory anaplastic lymphoma kinase (ALK)-positive unresectable inflammatory myofibroblastic tumour (IMT)
DHPC recipients	Paediatric oncologists, paediatric haemato-oncologists, ophtalmologists and hospital pharmacists. Final list of recipients to be further defined at national level, incl. professional societies and national associations, depending on the national healthcare system and in agreement with the respective national competent authority
Member States where the DHPC will be distributed	In all EU/EEA member states where Xalkori is marketed.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	10 June 2022
DHPC and communication plan (in English) agreed by CHMP	EMEA/H/C/002489/II/0072 CHMP opinion
Submission of translated DHPCs to the national competent authorities for review	EMEA/H/C/002489/II/0072 CHMP opinion + 7 calendar days
Agreement of translations by national competent authorities	EMEA/H/C/002489/II/0072 CHMP opinion + 14 calendar days
Dissemination of DHPC	EMEA/H/C/002489/II/0072 CE opinion