EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

# Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Active substance(s): deferasirox

Procedure No. EMEA/H/C/PSUSA/00000939/201710

Period covered by the PSUR: 01 Nov 2016 – 31 Oct 2017

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## Scientific conclusions

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

Cumulatively, 3 literature reported cases of drug-drug interaction between busulfan and deferasirox leading to increased busulfan exposure (via decreased busulfan clearance) were retrieved. In one case, deferoxamine was concomitantly administered and no de-challenge was performed. In the 2 other cases, a positive de-challenge without concomitant medications was reported. Some possible mechanisms for this drug-drug interaction have been proposed but however the exact mechanism remains unclear to date. Taking into account that supratherapeutic exposure to busulfan increases the risk for severe mucositis, sinusoidal obstructive syndrome, seizures, and pulmonary fibrosis and based on the available evidence of a drug-drug interaction between busulfan and deferasirox, the PRAC concluded that section 4.5 of the SmPC should be updated

Following the submission of a cumulative review during the evaluation of the present PSUR, a total of 19 serious cases (13 paediatric cases, 6 adult cases) of hepatic/renal damage without pre-existing altered function leading to hyperammonemia with no pertinent confounding factors were reported and considered as likely linked to deferasirox treatment. Most of these cases reported favourable evolution when deferasirox was discontinued (7 positive de-challenge, 8 cases with improvement after deferasirox discontinuation associated with symptomatic treatment, and 1 positive re challenge) with a compatible temporal association. All paediatric cases of but one and all adult cases reported encephalopathy and/or changes in consciousness/comatose states associated with the hyperammonemia context. Regarding volume depletion, 3 of the paediatric cases reported vomiting as a symptom (among which 1 reported rehydration therapy was provided) and 1 case reported dehydration. Among paediatric cases, 5 cases have an infectious context of acute illness: 1 case reported adenovirus infection, 1 case reported previously gastroenteritis with emesis while 3 cases reported upper respiratory tract infections among which 2 fatal cases in human respiratory syncytial virus positive patients. Among the 6 adult cases, 1 case reported vomiting and 2 cases reported melena as associated symptoms. Volume depletion may aggravated hepatic or renal failure, but could not be the sole cause in the development of hyperammonemia of hepatic or renal failure aetiology. Taking into account the available data, the PRAC concluded that the current warning on renal function and hepatic function in section 4.4 of the SmPC should be updated to inform healthcare professionals about severe forms of hepatic and/or renal failure associated with changes in consciousness in the context of hyperammonaemic encephalopathy with specific focus on paediatric patients and to recommend early dosage of ammonia levels in patients developing unexplained changes in mental status. In addition a new 2$^{nd}$ footnote is proposed to be included in section 4.8 of the SmPC for the ‘renal tubular function disorders’ and ‘hepatic failure’ adverse drug reactions regarding cases with hyperammonaemic encephalopathy and changes in consciousness.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing deferasirox 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 deferasirox the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing deferasirox is unchanged subject to the proposed changes to the product information

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