EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 March 2017
EMA/566488/2017
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): busulfan

Procedure No. EMEA/H/C/PSUSA/00000464/201607

Period covered by the PSUR: 9 July 2013 to 8 July 2016

Medicinal product no longer authorised

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Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for busulfan, the scientific conclusions of CHMP are as follows:

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

Seven literature reports have been published cumulatively concerning disturbance in dental development. In one article it was studied the role of busulfan in juvenile rats resulting in abnormal root development; a review of two cases of immunodeficiency disorders treated with busulfan and cyclophosphamide in which dental orthodontic treatment was provided; additional 2 case report of hypoplasia of permanent tooth germ is presented; one review assessed the long term effects of cytotoxic therapy concluding that tooth agenesis was more prevalent in patients treated with busulfan and cyclophosphamide; a study of 81 patients concluded that busulfan is as toxic as total body irradiation in causing disturbances in dental development; finally, a study of risk factors of tooth formation anomalies in paediatric cancers concluded that the high risk group of tooth agenesis was the subject with high dose chemotherapy under 4 years old. From the assessment of these articles, the causality of busulfan in the development of tooth hypoplasia is confirmed. Therefore, "tooth hypoplasia" should be added to the product information for both pharmaceutical forms.

Interaction between busulfan and metronidazol has been reported in literature reviews and post marketing cases. It is of particular interest the study of this interaction in three groups of patients in which higher plasma levels of busulfan were observed in the group receiving metronidazol prophylaxis during busulfan treatment than in those without metronidazoles. Therefore, this interaction should be included in the product information for both pharmaceutical forms.

The signal concerning interaction with deferasirox is refuted and it can be closed. This signal was open based on an isolated case from the literature and no additional cases have been reported. No pharmacokinetic explanation justifies this interaction. The signals concerning busulfan oral formulations and hepatic veno-oclusive disease risk in patients who have received prior radiation therapy /chemotherapy /HSCT, sterility, overdose treatment can be closed. These risks are assessed in the corresponding national procedures.

The MAH of Busilvex has responded to the question of "Thrombotic microangiopathy" (TMA) after hematopoietic cell transplantation (HCT) requested as supplementary information. A cumulative review of the literature and safety database has been performed. The occurrence of TMA is multifactorial and busulfan IV by itself cannot be considered as a main factor in the development of this reaction. Mainly studies from literature have shown that high busulfan *i.v.* doses in combination with other drugs in conditioning treatment previous HCT could be an important role in the development of TMA. As a conclusion, busulfan could be one risk factor of development TMA and a warning is section 4.4 of the Busilvex SmPC is considered warranted.

The warning for TMA after HCT only applies to one pharmaceutical form: the intravenous. Cases of TMA after high doses of busulfan *i.v.* in combination with other medicine as a conditioning treatment previous HCT have been seen after reviewing the literature and the cases retrieved in the safety database of the company. There are no cases with oral busulfan.

The benefit risk profile of the product remains favourable in the approved indications.

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

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Grounds for the variation to the terms of the marketing authorisation(s)

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

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

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

Medicinal product no longer authorised