20 July 2017
EMA/CHMP/542107/2017
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): bosentan

Procedure No. EMEA/H/C/PSUSA/00000425/201611

Period covered by the PSUR: 20 November 2015 to 19 November 2016

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Scientific conclusions

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

A study (Srinivas NR et al, 2016) showed that the exposure of tadalafil was reduced by bosentan. Bosentan (125 mg twice daily), a substrate of CYP2C9 and CYP3A4 and a moderate inducer of CYP3A4, CYP2C9 and possibly CYP2C19, reduced tadalafil (40 mg once per day) systemic exposure by 42% and Cmax by 27% following multiple dose co-administration. The efficacy of tadalafil in patients already on bosentan therapy has not been conclusively demonstrated. Tadalafil did not affect the exposure (AUC and Cmax) of bosentan or its metabolites. Therefore, the interaction between tadalafil and bosentan should be mentioned in the bosentan product information.

In addition, the following interactions which could have clinical relevance and which are already mentioned in bosentan SmPC should be added to the package leaflet: warfarin, simvastatin, ketoconazole and sildenafil.

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

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

On the basis of the scientific conclusions for bosentan the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing bosentan 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.