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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): rivaroxaban

Procedure No. EMEA/H/C/PSUSA/00002653/201709

Period covered by the PSUR: 16 September 2016 to 15 September 2017

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Scientific conclusions

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

Severe Cutaneous Adverse Reactions including Stevens-Johnson syndrome and Toxic Epidermal Necrolysis are already labelled in the Xarelto Summary of Product Characteristics (SmPC) sections 4.4 and 4.8. Based on the data submitted in this PSUR, the PRAC concluded that DRESS syndrome should be added to sections 4.4 and 4.8 (frequency "very rare"). Two literature cases provided evidence of a causal association between rivaroxaban and DRESS, considering a temporal association (time to onset within 10 days and 6 weeks respectively), and positive dechallenge. The established causal relationship between rivaroxaban and DRESS syndrome is considered sufficient for amending the SmPC.

Five post-marketing cases reported anaphylaxis with various degrees of severity. The present information in the SmPC needs to be amended to include "Anaphylactic reactions, including anaphylactic shock" in section 4.8 of the SmPC (frequency "very rare").

The interaction with fluconazole and with macrolide antibiotics (erythromycin and clarithromycin) is likely clinically insignificant in the absolute majority of patients but can potentially be significant in high risk patients. Since there have been reported cases with bleedings temporally associated with initiation of fluconazole and macrolide therapy in rivaroxaban treated patients, as a precautionary measure SmPC section 4.5 is slightly modified to express this uncertainty: "This increase is not considered clinically relevant" is requested to be changed to "The interaction with fluconazole/erythromycin/clarithromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients".

The MAH committed within LEG 0.39.3 to amend the SmPC during the ongoing PSUR procedure and to move the hepatic reactions included in the SOC Investigations to the SOC Hepatobiliary disorders in the tabulated list of ADRs in section 4.8. Moreover, the MAH agreed to move "Cholestasis, Hepatitis (incl. hepatocellular injury)" under the heading "Post-marketing observation" to the tabulated list of ADRs.

In accordance to the SmPC Guideline, all other information on adverse reactions under the heading "Post-marketing observation" ("angioedema and allergic oedema", "thrombocytopenia" and "SJS/ TEN") are also moved to the tabulated list of adverse reactions in section 4.8.

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 rivaroxaban the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing rivaroxaban 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.