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): dronedarone

Procedure No. EMEA/H/C/PSUSA/00001180/201907

Period covered by the PSUR: from 01 August 2016 to 31 July 2019

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Scientific conclusions

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

The potential drug-drug PK interaction between rivaroxaban and dronedarone and the risk of bleeding was assessed based on the review of the Sanofi global safety database (GSD), worldwide scientific literature and PK plausibility.

This review identified four cases with a positive de-challenge without identified co-medication or comorbidity that might provide alternative explanations. The increased bleeding risk resolved after discontinuation of dronedarone while rivaroxaban use continued.

The non-interventional retrospective cohort study (DRONEC09460) evaluating the "Concomitant Use of Dronedarone and Direct Oral Anticoagulants and the Risk of Major Bleeding in Patients with Nonvalvular Atrial Fibrillation" reported an increased risk of major bleeding, driven by GI bleeding with concomitant use of rivaroxaban with dronedarone compared to those taking rivaroxaban alone. For both dabigatran and rivaroxaban, major bleeding was higher among those taking dronedarone and dabigatran/rivaroxaban concomitantly compared to those taking dabigatran/rivaroxaban alone. This increased bleeding risk was not seen with concomitant use of apixaban and dronedarone, but this could be explained by the different non-metabolic clearance of apixaban that reduces the potential for drug-drug interaction.

Literature shows that in vitro there might be an 31% increase in rivaroxaban exposure due to inhibition of metabolism by dronedarone. A physiological based pharmacokinetic model showed a weak to moderate increase of the AUC of rivaroxaban in combination with dronedarone.

In relation to non-vit K antagonist regarding concomitant use with dronedarone the European Heart Rhythm Association guide 2018 states: "There are no interaction pharmacokinetic data available for rivaroxaban and apixaban but effects on their plasma levels can be anticipated based on P-gp and CYP3A4 interactions, calling for caution (i.e. 'yellow') or avoidance (for rivaroxaban)."

Furthermore, the SmPC of rivaroxaban mentions that active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Dronedarone is a moderate CYP3A4 inhibitor and a moderate -strong Pgp inhibitor.

In view of available data, concomitant use of dronedarone and rivaroxaban is expected to increase the plasma concentrations of rivaroxaban. The interaction may not be clinically relevant in most patients but could be significant in high-risk patients. Based on similar mechanism of action, the same can be expected for apixaban and edoxaban. As the level of evidence for drug-drug interactions between dronedarone and the different DOACs leading to increased exposure of the DOAC varies, slightly different recommendations on concomitant use with the different DOACs in section 4.5 of SmPC are recommended. A warning is also included in the corresponding part of the Package leaflet.

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 dronedarone the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing dronedarone is unchanged subject to the proposed changes to the product information.

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