Annex I

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

Scientific conclusions

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

In view of available data on the risks from clinical trials, the literature and in view of a plausible mechanism of action, as well as previous PSUSA outcomes, the PRAC considers a causal relationship for the drug-drug interaction between estradiol / nomegestrol acetate and glecaprevir/pibrentasvir is at least a reasonable possibility. The PRAC concluded that the sections 4.4. and 4.5 of the SmPC of product information of products containing estradiol / nomegestrol acetate should be amended accordingly.

In addition, in view of a literature data, a plausible mechanism of actions and previous PSUSA outcomes, the PRAC considers a causal relationship between estradiol / nomegestrol acetate and the exacerbation of symptoms of hereditary and acquired angioedema is at least a reasonable possibility.

The PRAC concluded that the product information of products containing estradiol / nomegestrol acetate should be amended accordingly.

Update of section 4.4 of the SmPC to add warnings on the drug-drug interaction with glecaprevir/pibrentasvir in the case of patients suffering from hepatitis C, as well as on the exacerbation of symptoms of hereditary and acquired angioedema.

Update of section 4.5 of the SmPC with details on the drug-drug interaction with glecaprevir/pibrentasvir.

The Package leaflet is updated accordingly.

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 estradiol / nomegestrol acetate the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing estradiol / nomegestrol acetate 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.