25 April 2014
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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): glycopyrronium bromide (indicated for chronic obstructive pulmonary disease)

Procedure No. PSUV/0004

Period covered by the PSUR: 29 March 2013 – 28 September 2013

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Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for Enurev Breezhaler, the scientific conclusions of PRAC are as follows:

During the reporting period one new safety signal – angioedema – was identified based on spontaneously reported cases. On the basis of the evaluation of this new signal MAH proposes to add angioedema as new ADR to the glycopyrronium CDS. The PRAC endorses the inclusion of angioedema in the CDS, and proposed inclusion also in the SmPC section 4.8 which was accepted by the MAH. An appropriate frequency for the ADR has been calculated in accordance with the SmPC guideline.

Upon request from PRAC, the MAH also evaluated the topic of hypersensitivity. Hypersensitivity reactions are described by terms included in the ADR section of the CDS: rash and angioedema. The data has shown that other symptoms of hypersensitivity occurred simultaneous with the angioedema and with the same time relations to drug administration. Symptoms include itching, redness, anaphylactic reaction, urticaria, generalized exanthema, dyspnea, irritative cough, flushing. As hypersensitivity reactions have been described for other medications in this class and hypersensitivity reactions with clinical manifestations of rash and angioedema has been observed with Enurev Breezhaler, the MAH suggested to amend the Contraindications and Warnings & Precautions sections of the Enurev CDS to add hypersensitivity. The PRAC endorsed addition of hypersensitivity in 4.4. of the SmPC and suggested similar text as given in the SmPCs for indacaterol. This wording was agreed on by the MAH.

Furthermore, the PRAC proposed that hypersensitivity is mentioned in section 4.8 in the SOC Immune system disorders with an appropriate frequency calculated from the clinical studies. Indeed, evidence provided by the MAH seems compatible with the assumption that there is a causal relationship between glycopyrronium and hypersensitivity. Inclusion of the information in section 4.8 seems helpful to patients and prescribers as the recognition of the hypersensitivity reaction is important to be able to initiate appropriate treatment. Furthermore, according to the SmPC guideline all reactions mentioned in section 4.4 should also be in section 4.8. Therefore, the PRAC recommends that the term is includes in section 4.8 as well. This was endorsed by the SmPC Advisory Group which was consulted on the matter. The MAH agreed upon this proposal.

Reports of medication errors suggested that most can be categorized as inadequate use of the device or drug. It is therefore suggested and endorsed by the PRAC that a passage is added to the Dosage and Administration under section 4.2 of the SmPC, saying: “Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it”. This was agreed by the MAH.

Therefore, in view of available data regarding medication errors, hypersensitivity and angioedema , the PRAC considered that changes to the product information were warranted.

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

Grounds recommending the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for Enurev Breezhaler, the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing the active substance glycopyrronium bromide is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation should be varied.