EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation

International non-proprietary name: rivastigmine

Procedure No. EMEA/H/C/PSUSA/00002654/201501

Period covered by the PSUR: 1 February 2014 – 31 January 2015

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Scientific conclusions

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

- **Cardiac arrhythmia**

Cardiac arrhythmia / bradycardia are listed adverse reactions for rivastigmine.

During the reporting period, 2 cases of torsade de pointe have been reported. Of these 2 cases of torsade de pointes with positive dechallenge after dose reduction or discontinuation of rivastigmine, the causal role of rivastigmine due to its bradycardia-related adverse event could not be ruled out despite the confounding factors in these cases (venlafaxine, tiapride).

Rivastigmine is known to induce bradycardia which constitutes a risk factor of QT prolongation and post-marketing cases of cardiac arrhythmia have been reported with the use of rivastigmine, especially in patients with other risk factors for QTc prolongation / Torsade de pointes (TdP) (concomitant treatments known to induce TdP, relevant cardiac disorders).

- **Nightmares**

During the reporting period 35 cases of nightmares were reported and 324 cumulatively (124 with oral formulations, 176 with patch formulations, 16 with unknown formulation and 4 with oral plus patch formulation). 26 relevant cases with positive dechallenge after discontinuation or dose reduction or positive rechallenge were identified. When documented the temporal relationship between the event onset and the start of rivastigmine indicates a causal relationship.

Due to the scientific literature, the significant proportional reporting ratio (PRR) for nightmares in EudraVigilance, data from clinical trials with oral formulation and post-marketing cases with both formulations, the PRAC agreed to add “nightmares” as adverse reaction in section 4.8 of the SmPC with frequency “not known” for the patch formulation and frequency “common” for oral formulations of rivastigmine-containing medicines.

Therefore, in view of available data regarding cardiac arrhythmia and nightmares, 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 rivastigmine the CHMP is of the opinion that the benefit-risk balance of the medicinal products containing rivastigmine is favourable subject to the proposed changes to the product information.

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