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): dulaglutide

Procedure No. EMEA/H/C/PSUSA/00010311/201709

Period covered by the PSUR: 19-March-2017 – 18-September-2017

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Scientific conclusions

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

A high number of cholelithiasis and cholecystitis cases have been reported with dulaglutide. In the 17 completed clinical trials there is a higher proportion of subjects with events of biliary tract AEs in the dulaglutide group (1.41 AEs per 100 p-y) compared to the placebo group (0.83 AEs per 100 p-y). The imbalance was primarily driven by events of "cholecystitis" and "cholelithiasis" (80%). The frequency of occurrence of cholelithiasis and cholecystitis is 0.66 % and 0.18%, respectively. Cases of cholelithiasis and cholecystitis from post marketing experience were reported.

Moreover, a mechanistic plausibility has been described for dulaglutide and gallbladder disease as follows: dulaglutide is a glucagon-like peptide 1 (GLP-1) receptor agonist. Responses expected from a GLP-1 receptor agonist include insulin release in the presence of elevated glucose concentrations, suppression of glucagon secretion, slowing of gastric emptying, and rapid and sustained weight loss. The gallbladder requires a cholecystokinin stimulus to empty. The presence of prolonged fasting or altered appetite causing reduced food intake might lessen or remove the stimulus to empty the gallbladder. Thus, concentrated bile may remain in the lumen of the gallbladder and become stagnant leading to the development of gallstones. In conclusion, the PRAC considered that cholelithiasis and cholecystitis should be added to the list of adverse drug reactions of dulaglutide.

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