NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by the Netherlands:

Product Name (s) in the referring Member State if applicable	*Metformin and metformin containing fixed-dose combinations*
Active substance(s)	*Metformin containing products*
Pharmaceutical form(s)	*All*
Strength(s)	*All*
Route of administration(s)	*All*
Marketing Authorisation Holders	*Various*

Background

Metformin containing products (as monocomponent or within a fixed-dose combinations (FDCs)) are authorised in the EU for the treatment of type 2 diabetes mellitus. Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Lactic acidosis is a known adverse drug reaction of metformin. It is a very rare, but serious (high mortality rate in the absence of prompt treatment), metabolic complication that can occur with metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with impaired renal failure or acute worsening of renal function (Lalau, Drug Saf. 2010 Sep 1;33(9):727-40).

Lactic acidosis is listed in the product information of metformin containing medicinal products in the EU and metformin containing products have been contra-indicated in patients with varying grades of renal impairment when creatinine clearance (CrCl) is < 60 ml/min.

During a recent Periodic Safety Update Report Single Assessment (PSUSA) procedure for metformin it became apparent that the product information of metformin containing products with regards to the cut-off value for creatinine clearance where metformin is contra-indicated, is not consistent between Member States, within Members States, and between metformin containing products. Recently, a worksharing variation procedure for the brand leader product Glucophage was finalised and concluded with a contra-indication in moderate (stage 3b) and severe renal failure or renal dysfunction (CrCl < 45 ml/min or eGFR < 45 ml/min/1.73m2). However, not all Member States were involved in the procedure. Currently, there are a number of metformin containing products, including FDCs that have been authorised via the centralised procedure, were moderate and severe renal impairment (CrCl < 60 mL/min) is still a contra-indication for use.

Moreover, European product information for metformin containing products significantly differs from recommendations in the majority of European and international treatment guidelines in diabetes mellitus that recommend the use of metformin in moderate renal impairment with a lower limit of eGFR $\geq$ 30 ml/min/1.73m^2.

Metformin is considered as the first choice in the treatment of DM type 2. It is generally accepted that it reduces the risk of cardiovascular disease and all-cause mortality in patients with normal or mildly reduced renal function (UKPDS). Epidemiological data (Roussel et al, Arch Intern Med 2010; 170(21):1892-9, Rachmani et al, Eur J Int Med 2002; 13:428-33) support that in patients with moderate renal insufficiency with eGFR $\geq$ 30 ml/min/1.73m^2, these benefits are maintained, although some controversial data exist for eGFR < 45 ml/min.1.73 m^2 (Ekström, 2012).

Issues to be considered

In view of the importance of metformin containing medicinal products in the treatment of type 2 diabetes, it is considered in the interest of the Union that the adequacy of the current product information of all metformin containing products is re-evaluated with respect to the risk of lactic acidosis and use in patients with renal failure. These patients form a large population which currently may have not access to the benefits of metformin across the Union (Roussel, Arch Intern Med. 2010;170(21):1892-1899).

It is the opinion of the Netherlands that the current data do not justify a contra indication in patients between 30 and 45 ml/min/m^2. Although controlled clinical data are sparse, metformin has been used regularly in these patients in daily practice without a marked increase in risk of lactic acidosis or other serious side effects (Christiansenet al, BMJ Open 2015;**5**:e008531).

Therefore, it should be assessed whether the use of metformin could be allowed in all patients with moderate renal insufficiency under certain conditions, such as a lower dose, not initiating treatment below 45 ml/min/m^2 and stopping treatment when risk factors are present, and to reinforce recommendations to mitigate the risks.

In view of the above, the Netherlands considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it gives its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be varied.

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Signed
Prof. dr. H.G.M. Leufkens
Medicines Evaluation Board

Date
25 January 2016