28 January 2016
EMA/CHMP/50774/2016

CHMP List of questions

To be addressed by the marketing authorisation holders for metformin containing medicinal products

Article 31 of Directive 2001/83/EC

Procedure number: EMEA/H/A-31/1432

Competact EMEA/H/A-31/1432/C/000655/0060, Ebymect EMEA/H/A-31/1432/C/004162/0007, Efficib EMEA/H/A-31/1432/C/000896/0078, Eucreas EMEA/H/A-31/1432/C/000807/0056, Glubrava EMEA/H/A-31/1432/C/000893/0045, Icandra EMEA/H/A-31/1432/C/001050/0056, Janumet EMEA/H/A-31/1432/C/000861/0077, Jentadueto EMEA/H/A-31/1432/C/002279/0029, Komboglyze EMEA/H/A-31/1432/C/002059/0030, Ristfor EMEA/H/A-31/1432/C/001235/0065, Synjardy EMEA/H/A-31/1432/C/003370/0013, Velmetia EMEA/H/A-31/1432/C/000862/0081, Vipdomet EMEA/H/A-31/1432/C/002654/0015, Vokanamet EMEA/H/A-31/1432/C/002656/0013, Xigduo EMEA/H/A-31/1432/C/002672/0018, Zomarist EMEA/H/A-31/1432/C/001049/0056

Active substance: metformin

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The marketing authorisation holders (MAHs) are requested to provide the following:

Efficacy

1. Please provide evidence of the therapeutic benefit of metformin for treatment of Type 2 diabetes mellitus (T2DM) in subjects with moderate renal insufficiency (eGFR between 30 and 60 ml/min/1.73m^2). Benefits may include improvement of glycaemic control and/or beneficial effects on micro or macrovascular complications.
2. Please present, based on literature/published data, expected systemic exposure of metformin in patients with T2DM and moderate renal insufficiency compared with normal renal function. These data should form the basis for dose recommendations in patients with renal impairment.

Safety

3. Please provide a summary of data that are relevant to estimate the risk of lactic acidosis with medicinal products containing metformin in patients with moderately impaired renal function. These data could include:

   - data from clinical trials (both placebo-controlled and active-controlled)
   - Spontaneous reports of cases of lactic acidosis with your metformin containing medicinal product(s);
   - Other relevant available data (i.e. pre-clinical data and other clinical data including epidemiological studies).

   The data should include, if possible, information on the reliability of the diagnosis of lactic acidosis as well as causality, age and sex of patient, dose and metformin plasma concentration, renal function (if possible divided by eGFR 30 – 45 ml/min/1.73m^2 and eGFR 46-60ml/min/1.73m^2), outcome, seriousness, concomitant medications, relevant medical history. Based on this information and if possible, high risk groups should be identified.
4. Please discuss and provide data with respect to any other safety issue, besides lactic acidosis , that might impact the benefit-risk in subjects with moderate renal impairment.

Product Information

5. Based on the responses to previous questions, please propose potential changes to the summary of product characteristics and package leaflet, with the aim to provide balanced information and minimize the risk of lactic acidosis and other possible safety issues in subjects with moderate renal insufficiency.

   Please also comment on how the impact of such measures should be monitored and assessed.