Annex IV

Scientific conclusions

Scientific conclusions

Metformin, alone or in combination with other medicines, is considered the first choice in the treatment for Type 2 diabetes mellitus (T2DM) and it is widely used in the EU. Currently the use of metformin in patients with renal failure is not harmonised across the EU, being contraindicated in patients with different stages of moderate renal failure depending on the member state and product. It is considered in the interest of the Union that the adequacy of the current recommendations for metformin containing products is re-evaluated with respect to the use in patients with moderate renal failure, taking into account the available information on the risk of lactic acidosis. These patients form a large population which currently may have not access to the benefits of metformin across the Union.

On 25 January 2016 the Netherlands therefore triggered a referral under Article 31 of Directive 2001/83/EC, and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of metformin containing products and to issue an opinion on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation

The benefits of metformin in the treatment of T2DM in patients with moderate renal impairment have been demonstrated in terms of the reduction of cardiovascular risk and all-cause mortality. Moreover, metformin treatment slows the further deterioration of renal function and provides additional significant micro-and macrovascular benefits in this patient population.

The most common side-effects observed in association with metformin use in diabetic individuals are mild to moderate gastrointestinal events including diarrhea, nausea, vomiting, abdominal pain, and decreased appetite. Apart from lactic acidosis, the overall safety profile of metformin in patients with moderate renal impairment is similar to the safety profile in patients with normal renal function.

The risk of lactic acidosis is very rare in clinical practice and in the majority of cases only observed in emergency care. In addition, although causality cannot be ruled out, other factors rather than metformin are most likely the causes of lactic acidosis.

Overall, metformin has been used safely in patients with moderate renal impairment at reduced doses without causing significant metformin or lactate plasma elevations. Moreover, recent clinical guidelines in the treatment of T2DM recommend the use of metformin in moderate renal impairment. As there is a clear relationship between renal function and metformin exposure, a recommendation for a daily dose of 2000 mg/day and 1000 mg/day dose in patients with moderate renal impairment stages 3a and 3b, respectively, can be concluded from the data provided.

In conclusion, the possible elevated risk of lactic acidosis could be sufficiently minimised in patients with moderate renal impairment (GFR greater than 30 ml/min) with a clear dosing recommendation, additional monitoring of GFR levels before and during treatment, and updated warnings and precautions in the SmPC and package leaflet. In addition, routine risk minimisation will be extended to include cumulative review of lactic acidosis in the PSURs and a targeted questionnaire.

Based on the review of all available data on safety and efficacy, the benefit-risk balance of medicinal products containing metformin remains favourable and it is recommended that the marketing authorisations are varied regarding the use in renal impairment.

In view of the above, the CHMP concluded that the benefit-risk balance of metformin containing medicinal products is favourable subject to changes to the product information as described above.

Grounds for CHMP opinion

Whereas

- The CHMP considered the procedure under Article 31 of Directive 2001/83/EC for metformin containing medicinal products.
- The CHMP reviewed the totality of the data submitted by the MAHs on the safety and efficacy of metformin containing medicinal products for the treatment of Type 2 diabetes mellitus in subjects with moderate renal impairment (GFR 30-59 ml/min) with a focus on the risk of lactic acidosis.
- The CHMP considered that there is evidence from clinical and epidemiological studies indicating the benefits of the use of metformin containing medicinal products in patients with moderate renal impairment (GFR 30-59 ml/min).
- The CHMP considered the evidence from epidemiological studies, which have shown that lactic acidosis is a very rare condition that occurs most often in patients with acute renal or cardiorespiratory illness or sepsis. Recent scientific data have concluded that the main causes of lactic acidosis are cardiogenic or hypovolemic shock, severe heart failure, severe trauma, and sepsis; therefore lactic acidosis is not primarily caused by metformin treatment.
- The CHMP considered that publications in the medical literature have shown that metformin at reduced dose may be safely used in patients with moderate renal impairment. In addition, published epidemiological studies indicate that metformin is often used in clinical practice in patients with moderate renal impairment as reflected in current clinical guidelines without a marked increase in risk of lactic acidosis or other serious side effects.
- The CHMP was of the view that the risk of lactic acidosis can be minimised in patients with moderate renal impairment with clear dosing recommendations, additional monitoring of GFR levels before and during treatment and updated warnings and precautions in the Summary of Product Characteristics (SmPC) and Package Leaflet (PL). In addition, routine pharmacovigilance activities will be extended to include a cumulative review and a targeted follow up questionnaire on lactic acidosis cases to be submitted in subsequent PSURs.

CHMP opinion

The CHMP, as a consequence, considers that the benefit-risk balance of metformin containing products remains favourable subject to the amendments to the product information.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for metformin containing products