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Use of metformin to treat diabetes now expanded to patients with moderately reduced kidney function

Recommendations for patients with kidney impairment updated in product information

The European Medicines Agency (EMA) has concluded that metformin-containing medicines can now be used in patients with moderately reduced kidney function (GFR [glomerular filtration rate] =30–59 ml/min) for the treatment of type 2 diabetes. The product information for these medicines will be updated to revise the current contraindication and give information about doses, monitoring and precautions in patients with reduced kidney function.

The recommendations are the result of a review by EMA of metformin-containing medicines following concerns that current scientific evidence does not justify a contraindication in patients with moderate reduction of kidney function. The current product information also varies between countries and products in the EU and is no longer consistent with clinical guidelines.

Metformin may increase the risk of a rare but serious complication called lactic acidosis, which occurs when naturally produced lactic acid builds up in the blood faster than it can be removed. Currently, the product information states that metformin must not be used in patients with reduced kidney function because these patients are considered to be at a higher risk of developing lactic acidosis as their kidneys do not remove metformin efficiently enough.

However, after considering the scientific literature, clinical data, epidemiological studies and clinical guidelines from medical bodies, EMA concluded that the large patient population with moderately reduced kidney function can benefit from use of metformin. Clear dosing recommendations and monitoring before and during treatment aim to minimise any possible increased risk in these patients. The contraindication for patients with severely reduced kidney function will remain (GFR less than 30 ml/min).

Companies marketing metformin-containing medicines will be requested to closely monitor and analyse future lactic acidosis cases and report these during upcoming periodic safety reviews in order to follow up on any changes in the frequency of this side effect. The product information for metformin-containing medicines will be updated to reflect the new recommendations and to ensure that the same advice is given to all patients in the EU.

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Information for patients

- Metformin is used on its own or with other medicines, together with diet and exercise, for the treatment of type 2 diabetes.
- Up to now, metformin medicines were not recommended for patients with moderate to severe reduction of kidney function. This recommendation has now changed to allow their use in patients with moderately reduced kidney function (GFR=30–59 ml/min). The dose of metformin should be adapted depending on the patient's kidney function. These medicines should still not be used in patients with severely reduced kidney function (GFR less than 30 ml/min).
- Patients with reduced kidney function may be at higher risk of lactic acidosis, a rare but serious side effect of metformin medicines caused by build-up of lactic acid in the blood. However, for patients with only moderately reduced kidney function any risk can be minimised by careful checking of dose and monitoring, allowing these patients to get the benefits these medicines can provide.
- Dehydration (significant loss of body fluids) increases the risk of developing lactic acidosis. If you experience severe vomiting, diarrhoea or fever, are exposed to heat, or drink less fluid than normal, you could become dehydrated. In these cases, stop taking metformin for a short time and speak with your doctor for further instruction.
- If you have any question or concern about your diabetes treatment or your kidney function level, speak with your doctor, nurse or pharmacist.

Information for healthcare professionals

- The review of metformin-containing medicines concluded that they can now be used in patients with moderately reduced kidney function (GFR=30–59 ml/min). Use in patients with GFR<30 ml/min is still contraindicated. GFR should be assessed before initiation of treatment and at least annually thereafter.
- Reduced doses should be considered for patients with moderate reduction of kidney function according to dosage recommendations provided in the updated product information. The product information also details risk factors for lactic acidosis which should be reviewed prior to and during treatment.
- Several fixed-dose combination products containing metformin are available in Europe (see below). If these products are used in patients with reduced kidney function, restrictions and efficacy regarding the other active substance in the combination, the feasibility of dose adjustment and the alternative of using individual tablets should be considered.
- Some fixed-dose combination products are still not recommended in patients with moderately reduced kidney function because the other active substance in the combination should not be used in these patients. For example, dapagliflozin/metformin (Ebymect, Xigduo) is not recommended in patients with GFR<60 ml/min; canagliflozin/metformin (Vokanamet) and empagliflozin/metformin (Synjardy) are not recommended in patients with GFR<45 ml/min and should not be started in patients with GFR<60 ml/min.
- These latest recommendations will result in harmonisation of product information about the use of metformin in patients with reduced kidney function and the precautions for lactic acidosis across the EU.

References

The review looked at data from a large number of studies including:

Ekström, N. et al., 'Effectiveness and safety of metformin in 51675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register', BMJ Open, 2012, 2:e001076.

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Inzucchi, S.E. et al., 'Metformin in patients with type 2 diabetes and kidney disease: a systematic review', JAMA, 2014, Vol. 312, p. 2668.

Richy, F.F. et al., 'Incidence of lactic acidosis in patients with type 2 diabetes with and without renal impairment treated with metformin: a retrospective cohort study', Diabetes Care, 2014, Vol. 37 (8), p. 2291.

Roussel, R. et al., 'Metformin use and mortality among patients with diabetes and atherothrombosis', Arch Intern Med, 2010, Vol. 170, p. 1892.

Salpeter, S.R. et al., 'Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus', Cochrane Database Syst Rev, 2010, CD00296.

Solini, A. et al., 'Age, renal dysfunction, cardiovascular disease, and antihyperglycemic treatment in type 2 diabetes mellitus: findings from the Renal Insufficiency and Cardiovascular Events Italian Multicenter Study', J Am Geriatr Soc, 2013, Vol. 61, p. 1253.

More about the medicine

Metformin is a medicine used on its own or in combination with other medicines for the treatment of type 2 diabetes. Metformin is used together with diet and exercise to improve control of blood glucose (sugar) levels. Medicines containing metformin alone have been authorised nationally in the EU since the 1960s, marketed as Glucophage and other tradenames. The following medicines containing combinations of metformin with other diabetes medicines in the same tablet have been authorised centrally through EMA: pioglitazone/metformin (Competact, Glubrava), dapagliflozin/metformin (Ebymect, Xigduo), sitagliptin/metformin (Efficib, Janumet, Ristfor, Velmetia), linagliptin/metformin (Jentadueto), saxagliptin/metformin (Komboglyze), alogliptin/metformin (Vipdomet), canagliflozin/metformin (Vokanamet), vildagliptin/metformin (Eucreas, Icandra, Zomarist) and empagliflozin/metformin (Synjardy). In addition, the combination glibenclamide/metformin (Glucovance) has been nationally authorised. For further information about the centrally authorised medicines, see here.

More about the procedure

The review of metformin-containing medicines was initiated on 28 January 2016 at the request of the Netherlands, under Article 31 of Directive 2001/83/EC.

The review has been carried out by the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which has adopted the Agency's

opinion. The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.

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