



## Metformin in patients with moderate renal impairment: reduce the dose

● The European Medicines Agency recommends reducing the dose of *metformin* for diabetic patients with moderate renal impairment. To reduce the risk of lactic acidosis, it is important to monitor the renal function of patients taking *metformin* and to pay attention to interactions.

*Metformin*, a biguanide, is the first-choice oral glucose-lowering drug in type 2 diabetes. In this situation, it appears to reduce mortality and prevent some of the complications of diabetes, while the adverse effects it provokes are usually acceptable. The adverse effects of *metformin* mainly consist of gastrointestinal disorders, which are frequent, and macrocytic anaemia. It can also provoke lactic acidosis, a rare but sometimes fatal adverse effect (1,2).

**Lactic acidosis with metformin: various risk factors.** *Metformin* is excreted unchanged in urine. Lactic acidosis is an adverse effect linked to *metformin* accumulation. It can occur in patients with renal failure and in situations that contribute to the development of renal failure, such as: dehydration; acute disease; and the use of drugs that are nephrotoxic or can provoke prerenal failure, such as nonsteroidal anti-inflammatory drugs, diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) or *aliskiren*. Other situations sometimes cause lactic acidosis in *metformin* users, in particular: acute alcohol intoxication, heart failure, respiratory failure, recent myocardial infarction or hepatic failure (1-4).

**Metformin in patients with moderate renal impairment: no consensus.** In patients with moderate renal impairment (i.e. whose glomerular filtration rate estimated by creatinine clearance is between 30 ml/min and 60 ml/min), there is no consensus over whether it is best to discontinue *metformin* or to continue *metformin* therapy at a lower dose (4). As of early 2017, in France, both of these options are suggested in the summaries of product characteristics (SPCs) for various *metformin*-containing drugs (5).

**According to the EMA doses for patients with moderate renal impairment should be reduced.**

In late 2016, given the disparities between SPCs within the European Union, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) conducted a review of clinical guidelines and data from the literature. It concluded that *metformin* has a positive harm-benefit balance in patients with moderate renal impairment, provided it is used at a lower dose: a maximum of 2000 mg per day when the glomerular filtration rate is between 45 ml/min and 59 ml/min, and a maximum of 1000 mg per day when it is between 30 ml/min and 44 ml/min. The CHMP recommended that *metformin* should remain contraindicated in patients with a glomerular filtration rate less than 30 ml/min (3,6).

**In practice** To minimise the risk of *metformin* overdose, attention should be paid to drug interactions, with regular monitoring of the patient's kidney function, and more frequent monitoring in high-risk situations. For patients with moderate renal impairment, if the choice is to continue *metformin* therapy, it makes sense to reduce the dose.

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### Selected references from Prescrire's literature search

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- 6- European Commission "Annexes-Metformin" 12 December 2016: 117 pages.



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