

## **FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function**

### **Safety Announcement**

**[4-8-2016]** The U.S. Food and Drug Administration (FDA) is requiring labeling changes regarding the recommendations for metformin-containing medicines for diabetes to expand metformin's use in certain patients with reduced kidney function. The current labeling strongly recommends against use of metformin in some patients whose kidneys do not work normally. We were asked<sup>1,2</sup> to review numerous medical studies regarding the safety of metformin use in patients with mild to moderate impairment in kidney function,<sup>3-14</sup> and to change the measure of kidney function in the metformin drug labeling that is used to determine whether a patient can receive metformin. We have concluded our review, and are requiring changes to the labeling of all metformin-containing medicines to reflect this new information.

**Health care professionals** should follow the latest recommendations when prescribing metformin-containing medicines to patients with impaired kidney function. **Patients** should talk to their health care professionals if they have any questions or concerns about taking metformin.

Metformin-containing medicines are available by prescription only and are used along with diet and exercise to lower blood sugar levels in patients with type 2 diabetes. When untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease. Metformin-containing medicines are available as single-ingredient products and also in combination with other drugs used to treat diabetes (see FDA Approved metformin-containing Medicines). The current drug labeling strongly recommends against metformin use in some patients whose kidneys do not work normally because use of metformin in these patients can increase the risk of developing a serious and potentially deadly condition called lactic acidosis, in which too much lactic acid builds up in the blood.

We have concluded from the review of studies published in the medical literature that metformin can be used safely in patients with mild impairment in kidney function and in some patients with moderate impairment in kidney function.<sup>3-6</sup> We are requiring changes to the metformin labeling to reflect this new information and provide specific recommendations on the drug's use in patients with mild to moderate kidney impairment.

We are also recommending that the measure of kidney function used to determine whether a patient can receive metformin be changed from one based on a single laboratory parameter (blood creatinine concentration) to one that provides a better estimate of kidney function in patients with kidney disease (i.e., glomerular filtration rate estimating equation (eGFR)).

Health care professionals and patients should report side effects involving metformin or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.

**FDA Approved metformin-containing Medicines\***

<b>Brand name</b>	<b>Active ingredient(s)</b>
Actoplus Met	metformin and pioglitazone
Actoplus Met XR	metformin extended release and pioglitazone
Avandamet	metformin and rosiglitazone
Fortamet	metformin extended release
Glucophage	metformin
Glucophage XR	metformin extended release
Glucovance	metformin and glyburide
Glumetza	metformin extended release
Invokamet	metformin and canagliflozin
Invokamet XR	metformin extended release and canagliflozin
Janumet	metformin and sitagliptin
Janumet XR	metformin extended release and sitagliptin
Jentadueto	metformin and linagliptin
Jentadueto XR	metformin extended release and linagliptin
Kazano	metformin and alogliptin
Kombiglyze XR	metformin extended release and saxagliptin
Prandimet	metformin and repaglinide
Riomet	metformin
Synjardy	metformin and empagliflozin
Synjardy XR	metformin extended release and empagliflozin
Xigduo XR	metformin extended release and dapagliflozin

\*These medicines are also available in multiple generic versions.

**Facts about metformin**

- Metformin-containing medicines are available by prescription only and are used along with diet and exercise to treat type 2 diabetes.
- Metformin helps control blood sugar in a number of ways. These include helping the body respond better to the insulin it makes naturally, decreasing the amount of sugar the liver makes, and decreasing the amount of sugar the intestines absorb from food.

- Metformin is available as a single-ingredient product and also in combination with other medicines used to treat diabetes. See FDA Approved metformin-containing Medicines.
- Common side effects of metformin include diarrhea, nausea, and upset stomach.
- Although rare, use of metformin can cause low blood sugar if patients do not eat enough, if they drink alcohol, or if they take other medicines to lower blood sugar.
- Approximately 14.4 million unique patients received a dispensed prescription for metformin or metformin-containing combination products from U.S. outpatient retail pharmacies in 2014.<sup>15</sup>

### **Additional Information for Patients**

- FDA is requiring manufacturers to revise the drug labeling of metformin-containing medicines to indicate that metformin may be safely used in some patients whose kidneys do not function normally. We are making this change after reviewing studies showing metformin's safety in patients with mild to moderate kidney impairment.<sup>3-6</sup> See FDA Approved metformin-containing Medicines.
- Before you take a medicine containing metformin, tell your health care professional if you have severe kidney problems or if you are going to have dye injected into a vein for an X-ray procedure.
- Do not take metformin if you have severe kidney problems.
- Read the patient [Medication Guide](#) or Patient Package Insert you receive with your prescription for a metformin-containing medicine. It explains the benefits and risks associated with the use of the medicine.
- Talk to your health care professional if you have any questions or concerns about metformin.
- Report side effects from metformin or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

### **Additional Information for Health Care Professionals**

- FDA is requiring manufacturers to revise the labeling of metformin-containing drugs to indicate that these products may be safely used in patients with mild to moderate renal impairment. See FDA Approved metformin-containing Medicines.
- We are also requiring manufacturers to revise the labeling to recommend that the measure of kidney function used to determine whether a patient can receive metformin be changed from one based on a single laboratory parameter (blood creatinine concentration) to one that provides a better estimate of renal function (i.e., glomerular filtration rate estimating equation (eGFR)). This is because in addition to blood creatinine concentration, the glomerular filtration rate takes into account additional parameters that are important, such as the patient's age, gender, race and/or weight.

- The labeling recommendations on how and when kidney function is measured in patients receiving metformin will include the following information:
  - Before starting metformin, obtain the patient's eGFR.
  - Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m<sup>2</sup>.
  - Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m<sup>2</sup> is not recommended.
  - Obtain an eGFR at least annually in all patients taking metformin. In patients at increased risk for the development of renal impairment such as the elderly, renal function should be assessed more frequently.
  - In patients taking metformin whose eGFR later falls below 45 mL/minute/1.73 m<sup>2</sup>, assess the benefits and risks of continuing treatment. Discontinue metformin if the patient's eGFR later falls below 30 mL/minute/1.73 m<sup>2</sup>.
  - Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/minute/1.73 m<sup>2</sup>; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.
- Encourage patients to read the [Medication Guide](#) or Patient Package Insert they receive with their prescriptions for metformin-containing drugs.
- Report adverse events involving metformin or other drugs to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

## Data Summary

Since FDA approved metformin in 1995, its labeling has included a contraindication against use in some patients with renal disease or dysfunction. We recently reviewed publications in the medical literature that show that metformin may be safely used in patients with mild to moderate renal impairment.<sup>3-6</sup> In addition, published clinical trials, population-based studies, and retrospective case series in the United States and abroad indicate that metformin is often used in clinical practice outside of the current labeling indications and is prescribed to patients with mild to moderate chronic kidney disease.<sup>7-14</sup>

## References

1. Regulations.gov. Yale University Citizen Petition. <http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-0298-0002>. Published April 3, 2013. Accessed March 30, 2016. A copy of the response is available at [www.regulations.gov](http://www.regulations.gov) under Docket No. FDA-2013-P-0298.
2. Regulations.gov. James Flory MD, MSCE, et al (New York Presbyterian Hospital, Weill Cornell) Citizen Petition.

<http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-1052-0001>. Published October 11, 2012. Accessed March 30, 2016. A copy of the response is available at [www.regulations.gov](http://www.regulations.gov) under Docket No. FDA-2012-P-1052.

3. Rachmani R, Slavachevski I, Levi Z, Zadok B, Kedar Y, Ravid M. Metformin in patients with type 2 diabetes mellitus: reconsideration of traditional contraindications. *Eur J Intern Med* 2002;13:428.
4. Kamber N, Davis WA, Bruce DG, Davis TM. Metformin and lactic acidosis in an Australian community setting: the Fremantle Diabetes Study. *Med J Aust* 2008;188:446-9.
5. Roussel R1, Travert F, Pasquet B, Wilson PW, Smith SC Jr, Goto S, et al. Metformin use and mortality among patients with diabetes and atherothrombosis. *Arch Intern Med* 2010;170:1892-9.
6. Ekström N, Schiöler L, Svensson AM, Eeg-Olofsson K, Miao Jonasson J, Zethelius B, et al. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. *BMJ Open* 2012;2.pii:e001076.
7. Emslie-Smith AM, Boyle DI, Evans JM, Sullivan F, Morris AD; DARTS/MEMO Collaboration. Contraindications to metformin therapy in patients with Type 2 diabetes--a population-based study of adherence to prescribing guidelines. *Diabet Med* 2001;18:483-8.
8. Holstein A, Nahrwold D, Hinze S, Egberts EH. Contra-indications to metformin therapy are largely disregarded. *Diabet Med* 1999;16:692-6.
9. Horlen C, Malone R, Bryant B, Dennis B, Carey T, Pignone M, et al. *JAMA* 2002;287:2504-5.
10. Kennedy L, Herman WH; GOAL A1C Study Team. *Diabetes Care* 2005;28:922-4.
11. Calabrese AT, Coley KC, DaPos SV, Swanson D, Rao RH. Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. *Arch Intern Med* 2002;162:434-7.
12. Warren RE, Strachan MW, Wild S, McKnight JA. Introducing estimated glomerular filtration rate (eGFR) into clinical practice in the UK: implications for the use of metformin. *Diabet Med* 2007;24:494-7.
13. Sulkin TV, Bosman D, Krentz AJ. Contraindications to metformin therapy in patients with NIDDM. *Diabetes Care* 1997;20:925-8.

14. Vasisht KP, Chen SC, Peng Y, Bakris GL. Limitations of metformin use in patients with kidney disease: are they warranted? *Diabetes Obes Metab* 2010;12:1079-83.
  
15. IMS Health, Total Patient Tracker. Year 2014. Extracted September 2015.