

FDA Drug Safety Communication: FDA warns that DPP-4 inhibitors for type 2 diabetes may cause severe joint pain

Safety Announcement

[8-28-2015] The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines sitagliptin, saxagliptin, linagliptin, and alogliptin may cause joint pain that can be severe and disabling. We have added a new *Warning and Precaution* about this risk to the labels of all medicines in this drug class, called dipeptidyl peptidase-4 (DPP-4) inhibitors.

Patients should not stop taking their DPP-4 inhibitor medicine, but should contact their health care professional right away if they experience severe and persistent joint pain. Health care professionals should consider DPP-4 inhibitors as a possible cause of severe joint pain and discontinue the drug if appropriate.

DPP-4 inhibitors are used along with diet and exercise to lower blood sugar in adults with type 2 diabetes. When untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease. These medicines are available as single-ingredient products and in combination with other diabetes medicines such as metformin (see Table 1 below).

In a search of the [FDA Adverse Event Reporting System \(FAERS\) database](#) and the medical literature,¹⁻⁴ we identified cases of severe joint pain associated with the use of DPP-4 inhibitors. Patients started having symptoms from 1 day to years after they started taking a DPP-4 inhibitor. After the patients discontinued the DPP-4 inhibitor medicine, their symptoms were relieved, usually in less than a month. Some patients developed severe joint pain again when they restarted the same medicine or another DPP-4 inhibitor.

We urge health care professionals and patients to report side effects involving DPP-4 inhibitors to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

Table 1. List of FDA-approved DPP-4 inhibitors

Brand name	Active ingredient(s)
Januvia	sitagliptin
Janumet	sitagliptin and metformin
Janumet XR	sitagliptin and metformin extended release
Onglyza	saxagliptin
Kombiglyze XR	saxagliptin and metformin extended release
Tradjenta	linagliptin
Glyxambi	linagliptin and empagliflozin
Jentaduetto	linagliptin and metformin
Nesina	alogliptin
Kazano	alogliptin and metformin
Oseni	alogliptin and pioglitazone

Facts about Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

- DPP-4 inhibitors are a class of prescription medicines that are used with diet and exercise to control high blood sugar in adults with type 2 diabetes.
- Medicines in the DPP-4 inhibitor class include sitagliptin, saxagliptin, linagliptin, and alogliptin. They are available as single-ingredient products and in combination with other diabetes medicines such as metformin (see Table 1 in the Safety Announcement section for a complete list of FDA-approved DPP-4 inhibitors).
- DPP-4 inhibitors lower blood sugar by helping the body increase the level of the hormone insulin after meals. Insulin helps move sugar from the blood into the tissues so the body can use the sugar to produce energy and keep blood sugar levels stable.
- In addition to severe joint pain, other possible side effects of DPP-4 inhibitors include inflammation of the pancreas, low blood sugar when this class of medicines is combined with other prescription medicines used to treat diabetes, and allergic reactions.

Additional Information for Patients

- Some patients who take the type 2 diabetes medicines called dipeptidyl peptidase-4 (DPP-4) inhibitors can develop joint pain that can be severe. See Table 1 in the Safety Announcement section for a list of FDA-approved DPP-4 inhibitors.
- Contact your health care professional right away if you develop severe and persistent joint pain while taking one of these medicines. Do not stop taking your DPP-4 inhibitor medicine without first talking to your health care professional.
- Read the patient Medication Guide you receive with your DPP-4 inhibitor prescription. It explains the benefits and risks associated with the use of the medicine. You may access Medication Guides by clicking on this [link](#).
- Talk to your health care professional if you have questions or concerns about your diabetes medicines.

- Report side effects from DPP-4 inhibitors 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

- Severe and disabling joint pain has been reported with the use of dipeptidyl peptidase-4 (DPP-4 inhibitors). The time to onset of symptoms following initiation of drug therapy varied from 1 day to years. Patients experienced relief of symptoms upon discontinuation of the medication. Some patients had a recurrence of severe joint pain when restarted on either their original DPP-4 inhibitor medication or another DPP-4 inhibitor.
- Consider DPP-4 inhibitors as a possible cause for any patient who presents with severe and persistent joint pain, and consider discontinuation of therapy with this class of drugs.
- Encourage patients to read the Medication Guide they receive with their DPP-4 inhibitor prescriptions.
- Report adverse events involving DPP-4 inhibitors to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

In a search of the [FDA Adverse Event Reporting System \(FAERS\) database](#), we identified 33 cases of severe arthralgia reported with the use of dipeptidyl peptidase-4 (DPP-4) inhibitors from October 16, 2006, approval date of the first DPP-4 inhibitor, through December 31, 2013. Each case involved the use of one or more DPP-4 inhibitor. Sitagliptin (n=28) was the most frequently reported, followed by saxagliptin (n=5), linagliptin (n=2), alogliptin (n=1), and vildagliptin (n=2); vildagliptin is not marketed in the United States. In five cases, the patient experienced severe arthralgia with two different DPP-4 inhibitors. All 33 patients experienced arthralgia that resulted in a substantial reduction in their prior level of activity, including 10 patients who were hospitalized due to disabling joint pain. In 22 cases, symptoms appeared within 1 month of initiation of treatment with a DPP-4 inhibitor. In 20 of the 33 cases, the DPP-4 inhibitor was suspected as a possible cause of arthralgia and was discontinued within a month following the onset of symptoms. However, 8 of the remaining 13 cases reported a period of 44 days to 1 year between the onset of symptoms and discontinuation of the DPP-4 inhibitor. In 23 of the 33 cases, symptoms resolved less than 1 month after discontinuation of the drug.

Reports of eight of the 33 cases documented a positive rechallenge. In these eight cases, individuals discontinued treatment, experienced a resolution of symptoms, restarted therapy with a DPP-4 inhibitor (a different member of the class in six of the eight cases), experienced the reappearance of the arthralgia, and subsequently, experienced resolution of the symptoms when DPP-4 inhibitor therapy was again discontinued. Twenty-one of the 33 patients were treated for arthritis with drug therapies that included corticosteroids, nonsteroidal anti-inflammatory drugs, methotrexate, and immune-modulating drugs.

We reviewed the clinical details in the FAERS cases to determine whether the severe joint pain could have been caused by an autoimmune condition rather than the DPP-4 inhibitors. Ten of the 33 cases reported fever and chills, rash, and swelling, which are suggestive of an immunological reaction. Of the 13 cases with available results of laboratory assays for systemic autoimmune disorders, 8 reported a negative or normal test result. Five cases reported positive test results: antinuclear antibody (n=2), erythrocyte sedimentation rate (n=1), C-reactive protein (n=1), and antinuclear cytoplasmic antibody (n=1). However, none of these tests are specific for a particular autoimmune condition that can cause severe joint pain.

We also searched the medical literature and identified seven case reports,¹⁻⁴ two of which were also identified in the FAERS database.^{3,4} All seven reports described patients who developed arthralgia after starting therapy with either sitagliptin (n=6) or vildagliptin (n=1). In six cases, patients had partial or complete resolution of symptoms within 6 weeks of discontinuing the drug. Only one case reported the pain to be disabling, and none reported the need for hospitalization.

References

1. Crickx E, Marroun I, Veyrie C, Le Beller C, Schoindre Y, Bouilloud F, et al. DPP4 inhibitor-induced polyarthritis: a report of three cases. *Rheumatol Int* 2014;34:291-2.
2. Yokota K, Igaki N. Sitagliptin (DPP-4 inhibitor)-induced rheumatoid arthritis in type 2 diabetes mellitus: a case report. *Intern Med* 2012;51:2041-4.
3. Sasaki T, Hiki Y, Nagumo S, Ikeda R, Kimura H, Yamashiro K, et al. Acute onset of rheumatoid arthritis associated with administration of a dipeptidyl peptidase-4 (DPP-4) inhibitor to patients with diabetes mellitus. *Diabetol Int* 2010;1:90-2.
4. Chaicha-Brom T, Yasmeen T. DPP-IV inhibitor-associated arthralgias. *Endocr Pract* 2013;19:377.