

FDA strengthens warning that untreated constipation caused by schizophrenia medicine clozapine (Clozaril) can lead to serious bowel problems  
*Risk increased at higher doses or when taken with other constipating medicines*

## 01-28-2020 FDA Drug Safety Communication

### What safety concern is FDA announcing?

The Food and Drug Administration (FDA) is strengthening an existing warning that constipation caused by the schizophrenia medicine clozapine (Clozaril, Fazacllo ODT, Versacloz, generics) can, uncommonly, progress to serious bowel complications. This can lead to hospitalization or even death if constipation is not diagnosed and treated quickly. Constipation is a frequent and known side effect of clozapine, but serious and fatal events continue to be reported.

Clozapine affects how the intestines (bowels) function in the majority of patients. It produces effects ranging from constipation (trouble having a bowel movement), which is a common occurrence, to serious but uncommon bowel problems, including complete blockage of the bowel. We found that because of the way clozapine works this risk is greater with clozapine than with the other schizophrenia medicines in its drug class. The risk is further increased at higher doses of clozapine and when it is co-prescribed with a type of medicine called anticholinergics, which can slow the movement in the intestines, and other medicines that cause constipation, including opioids. Many different kinds of medicines have these anticholinergic effects.

### What is FDA doing?

We are requiring a new warning and updates about this risk to be added to the [prescribing information](#) of all clozapine products. As part of FDA's routine monitoring, we will continue to monitor clozapine and will report updated information to the public if it becomes available.

### What is clozapine and how can it help me?

Clozapine is a medicine that has been used for more than 40 years to treat schizophrenia in patients whose symptoms are not controlled with standard treatment. Symptoms of schizophrenia include hearing voices, seeing things that are not there, and being suspicious or withdrawn. Clozapine is also effective in reducing the risk of suicidal thinking and self-harm in patients with schizophrenia or schizoaffective disorder. It is sold under the brand names Clozaril, Fazacllo ODT, and Versacloz, and as generics by many different drug companies.

### What should patients and caregivers do?

Patients may not feel or be aware of constipation symptoms. However, you should contact your health care professional if your bowel movements are less frequent than normal for you, especially if you do not have a bowel movement at least three times a week, you have hard or dry

stools, or you have difficulty passing gas. You should contact your health care professional right away if you have symptoms which can be associated with serious bowel problems such as nausea and vomiting, bloating or belly swelling, or belly pain.

To prevent constipation, you should eat more fruits, vegetables, and grains that are high in fiber; drink plenty of water and other liquids; and get enough exercise. You may also need to take a laxative, so ask a health care professional which type of laxative is right for you. You should not stop taking your clozapine medicine without first talking with your health care professional, as stopping treatment can cause your schizophrenia symptoms to return or worsen.

### **What should health care professionals do?**

Health care professionals should evaluate bowel function before starting a patient on clozapine and avoid co-prescribing clozapine with other anticholinergic medicines that can cause gastrointestinal hypomotility. Advise patients frequently of the significant risk of constipation and life-threatening bowel issues and the need to stay hydrated to prevent constipation.

Question patients about the frequency and quality of their bowel movements throughout treatment. Advise patients to contact a health care professional right away if they have difficulty having a bowel movement or passing stools, do not have a bowel movement at least three times a week or less than their normal frequency, or are unable to pass gas. Monitor patients for symptoms of potential complications associated with gastrointestinal hypomotility such as nausea, abdominal distension or pain, and vomiting. Consider prophylactic laxative treatment when starting clozapine in patients with a history of constipation or bowel obstruction.

### **What did FDA find?**

We reviewed the period from 2006 to 2016 and identified 10 cases describing constipation that progressed to serious bowel problems resulting in hospitalization, surgery, or death. These included death of the colon wall (necrotizing colitis), blockage of blood flow to the intestines (intestinal ischemia), death of part of the intestine (intestinal necrosis), and abdominal distention leading to bowel obstruction (volvulus). This number includes only cases submitted to FDA\* or those found in the medical literature, so there may be additional cases about which we are unaware (see Data Summary).

We previously communicated about clozapine in [September 2015](#) (changes in neutropenia monitoring; single, shared REMS program) and [February 2011](#) (risk of abnormal muscle movements and withdrawal symptoms in newborns).

\*The cases were reported to the [FDA Adverse Event Reporting System \(FAERS\)](#).

### **What is my risk?**

All medicines have side effects even when used correctly as prescribed, but in general the benefits of taking a medicine outweigh these risks. It is important to know that people respond differently to all medicines depending on their health, other medicines they are taking, the diseases they have, genetics, and many other factors. As a result, we cannot determine the likelihood that someone will experience these side effects when taking clozapine. Your personal health care professionals know you best, so always tell them about all other medicines you are

taking, including over the counter medicines, and if you experience any side effects while taking your medicines.

### **How do I report side effects from clozapine?**

To help FDA track safety issues with medicines, report adverse events involving clozapine or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.

### **Facts about Clozapine (Clozaril, Fazaclo ODT, Versacloz)**

- Clozapine is a medicine used to treat schizophrenia in patients whose symptoms are not controlled with standard antipsychotic medicines.
- Clozapine is also effective in reducing the risk of suicidal thinking and self-harm in patients with schizophrenia or schizoaffective disorder.
- Clozapine has strong effects that can impair movement through the bowels, causing a blockage.
- Clozapine is available as tablets taken by mouth. It is sold under the brand names Clozaril, Fazaclo ODT, and Versacloz, and as generics by many different drug companies.
- Common side effects in addition to constipation include dry mouth, drooling, drowsiness, lightheadedness, shaking or tremor, and blurred vision.
- In 2018, an estimated 782,000 clozapine prescriptions were dispensed from U.S. outpatient retail pharmacies, which was a 2.3% decline from 2016 (800,000 clozapine prescriptions).<sup>1</sup>

### **Additional Information for Patients and Caregivers**

- FDA is strengthening an existing warning that constipation caused by the schizophrenia medicine clozapine (Clozaril, Fazaclo ODT, Versacloz) can progress to serious bowel problems. This can lead to hospitalization or even death if constipation is not diagnosed and treated quickly.
- Constipation is a frequent and known side effect of clozapine, but serious bowel problems continue to be reported, although they are uncommon.
- The risk is greater with clozapine than the other schizophrenia medicines we reviewed in its drug class because of the way clozapine works.
- The risk is further increased at higher doses of clozapine or when it is co-prescribed with a type of medicine called anticholinergics, which can slow the movement in the intestines, and other medicines that cause constipation, including opioids.
- As a result, we are requiring a new warning and updates about this risk to be added to the [prescribing information](#) of all clozapine products.
- You may not feel or be aware of constipation symptoms. Contact your health care professional if you are having bowel movements at less than your normal frequency, especially if it is less than three times a week, you have hard or dry stools, or you have difficulty passing gas. Other symptoms associated with serious bowel problems include nausea, bloating or belly swelling, belly pain, and vomiting.
- To prevent [constipation](#), eat more fruits, vegetables and grains, which are high in fiber. Avoid bulking agents such as psyllium (Metamucil) or fiber supplements unless directed by your health care professional.

- Drink plenty of water and other liquids and get enough exercise. You may also need to take a [laxative](#), so ask your health care professional which type of laxative is right for you.
- Do not stop taking your medicine without first talking to your health care professional as stopping treatment can cause your schizophrenia symptoms to worsen or return.
- Read the patient information leaflet when you receive a prescription for clozapine, which will explain this new information and important things that you need to know about the medicine. These include the side effects, what the medicine is used for, how to take and store it properly, and other things to watch out for when you are taking the medicine.
- To help FDA track safety issues with medicines, report side effects from clozapine 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 strengthening an existing warning that constipation caused by the schizophrenia medicine clozapine (Clozaril, Fazacllo ODT, Versacloz) can progress to serious bowel complications. This can lead to hospitalization or even death if constipation is not diagnosed and treated quickly.
- Clozapine impairs bowel function in the majority of patients. It produces effects ranging from constipation (common) to complete bowel obstruction, paralytic ileus and intestinal ischemia or infarction (uncommon). Constipation is a frequent and known side effect of clozapine, but serious and fatal events continue to be reported.
- The risk is greater with clozapine than the other schizophrenia medicines we reviewed in its drug class because of clozapine’s potent anticholinergic activity.
- The risk is further increased at higher doses of clozapine or when it is co-prescribed with anticholinergic agents and other medicines that cause constipation, including opioids.
- As a result, we are requiring a new warning and updates about this risk to be added to the [prescribing information](#) of all clozapine products.
- Be aware that subjective symptoms of constipation reported by patients may not accurately reflect gastrointestinal hypomotility; therefore, it is essential to question patients regarding the frequency and character of bowel movements and any changes.
- Avoid co-prescribing clozapine with other anticholinergic medicines that can cause gastrointestinal hypomotility.
- Consider prophylactic use of laxatives when starting clozapine in high-risk patients.
- If constipation is identified, promptly treat it with laxatives and adjust as necessary. Consult a gastroenterologist in more serious cases.
- Encourage appropriate hydration, physical activity, and foods that are high in fiber.
- Educate patients and caregivers on the risks, prevention, and treatment of clozapine-induced constipation, including medicines to avoid such as other anticholinergic medicines.
- Emphasize that prompt attention and treatment for constipation and other gastrointestinal symptoms is critical to preventing serious complications.
- Encourage patients to read the patient information leaflet they receive with their clozapine prescription, so they are aware of this additional information about the medicine.

- To help FDA track safety issues with medicines, report adverse events involving clozapine or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.

### Data Summary

FDA identified 10 cases of constipation that progressed to serious complications with clozapine use reported in the [FDA Adverse Event Reporting System \(FAERS\) database](#) from July 21, 2006, through July 20, 2016, and in the medical literature from July 21, 2006, through August 2, 2016. These cases resulted in hospitalization, surgery, and five deaths. Adverse events included necrotizing colitis<sup>2-5</sup> (n=4), intestinal ischemia or necrosis<sup>6-8</sup> (n=5), and volvulus (n=1). The total daily dose of clozapine administered ranged from 200 mg to 600 mg, with a median daily dose of 400 mg. The time to onset of serious bowel events ranged from 3 days to 6 months, with a median of 46 days. A preliminary review of additional FAERS data reported from July 21, 2016, through the end of 2019 found similar findings. Clozapine can do this alone; in contrast, serious complications of constipation have been identified with other antipsychotics (e.g., olanzapine) only when they were used with other anticholinergic medicines.

A New Zealand study of 37 patients conducted by Every-Palmer et al.<sup>2</sup> objectively assessed and confirmed clozapine-induced gastrointestinal hypomotility by measuring colonic transit time (CTT) using radiopaque markers. The study reviewed the effects of clozapine (monotherapy and combination antipsychotic therapy, 20 patients) and non-clozapine antipsychotics (monotherapy and combination antipsychotic therapy, 17 patients) and concluded that nearly all patients receiving clozapine had increased CTTs, but most non-clozapine treated patients did not. An exposure-related increase in CTT was seen (that is, higher CTT with higher clozapine levels); however, patients did not report the hypomotility as subjective symptoms of constipation. The median CTT in patients treated with clozapine was more than four times longer than in patients not prescribed clozapine (105 hours vs. 23 hours, respectively).

### References

1. IQVIA National Prescription Audit™ (NPA) Database. Years 2016 and 2018. Data Extracted December 2019.
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3. Leong QM, Wong KS, Koh DC. Necrotising colitis related to clozapine? A rare but life threatening side effect. *World J Emerg Surg.* 2007;2:21.
4. Martinez Diaz-Caneja C, González-Molinier M, Galindo JC, Iñiguez MM. Severe Bowel Ischemia Due to Clozapine with Complete Remission After Withdrawal. *J Clin Psychopharm.* 2010;30(4):463-5.
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6. Alam HB, Fricchione GL, Guimaraes ASR, Zukerber LR. Case 31-2009: A 26-year-Old Man with Abdominal Distention and Shock. *N Engl J Med.* 2009;361:1487-96.
7. Naravadi VVR and Valluru N. Clozapine-induced gastrointestinal hypomotility (CIGH): An under-recognized serious side effect. *Am J Gastroenterol.* 2014;109(Suppl 2):S430.
8. Parakkal D, DeLemos D, Ehrenpreis E. Rapidly Progressive Shock and Death from Clozapine-Induced Toxic Megacolon: Lessons Still to be Learned. *Am J Gastroenterol.* 2011;106(Suppl 2):S340.

9. Every-Palmer S, Nowitz M, Stanley J, Grant E, Huthwaite M, Dunn H, et al. Clozapine-treated Patients Have Marked Gastrointestinal Hypomotility, the Probable Basis of Life-Threatening Gastrointestinal Complications: A Cross Sectional Study. EBioMedicine. 2016;5:125-34.

#### **Related Information**

- [Constipation](#)
- [Laxatives](#)
- [Information on Clozapine](#)
- [REMS@FDA](#)
- [Atypical Antipsychotic Drugs Information](#)
- [Information on Conventional Antipsychotics](#)
- [FDA Drug Safety Communication: FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine; approves new shared REMS program for all clozapine medicines](#)
- [The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective](#)
- [Think It Through: Managing the Benefits and Risks of Medicines](#)