



U.S. Food and Drug Administration
Protecting and Promoting Your Health

Drug Safety Communications

FDA Drug Safety Communication: FDA warns of serious slowing of the heart rate when antiarrhythmic drug amiodarone is used with hepatitis C treatments containing sofosbuvir (Harvoni) or Sovaldi in combination with another Direct Acting Antiviral drug

Safety Announcement

[03-24-2015] The U.S. Food and Drug Administration (FDA) is warning that serious slowing of the heart rate can occur when the antiarrhythmic drug amiodarone is taken together with either the hepatitis C drug Harvoni (ledipasvir/sofosbuvir) or with Sovaldi (sofosbuvir) taken in combination with another direct acting antiviral for the treatment of hepatitis C infection. We are adding information about serious slowing of the heart rate, known as symptomatic bradycardia, to the Harvoni and Sovaldi labels. We are recommending that health care professionals should not prescribe either Harvoni or Sovaldi combined with another direct acting antiviral, such as the investigational drug daclatasvir or Olysio (simeprevir), with amiodarone. Patients should not stop taking any of their medicines without first talking to their health care professionals.

Harvoni and Sovaldi are used to treat chronic hepatitis C, a viral infection that can last a lifetime and lead to serious liver problems, including cirrhosis or liver cancer. These drugs reduce the amount of hepatitis C virus in the body by preventing the virus from multiplying within the body.

Our review of submitted postmarketing adverse event reports found that patients can develop a serious and life-threatening symptomatic bradycardia when either Harvoni or Sovaldi combined with another direct-acting antiviral is taken together with amiodarone. The reports included the death of one patient due to cardiac arrest and three patients requiring placement of a pacemaker to regulate their heart rhythms. The other patients recovered after discontinuing either the hepatitis C drugs or amiodarone, or both (see Data Summary). The cause of these events could not be determined.

Information about this serious risk of bradycardia has been added to the *Warnings and Precautions*, *Drug Interactions*, and *Postmarketing Experience* sections of the drug labels for Harvoni and Sovaldi. We will continue to monitor Harvoni and Sovaldi for risks of serious symptomatic bradycardia and further investigate the reason why the use of amiodarone with these hepatitis C drugs led to the heart-related events.

Health care professionals should not prescribe either Harvoni or Sovaldi combined with another direct-acting antiviral drug with amiodarone. However, in cases where alternative treatment options are unavailable, we recommend heart monitoring in an inpatient hospital setting for the first 48 hours. Subsequently, monitoring in a doctor's office or self-monitoring of the heart rate should be done every day through at least the first 2 weeks of treatment.

Patients taking either Harvoni or Sovaldi combined with another direct-acting antiviral drug with amiodarone should seek medical attention right away if they experience signs or symptoms of symptomatic bradycardia such as:

- Near-fainting or fainting
- Dizziness or light-headedness
- Malaise
- Weakness
- Excessive tiredness
- Shortness of breath
- Chest pains
- Confusion or memory problems

We urge health care professionals and patients to report side effects involving Harvoni, Sovaldi, or amiodarone to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

Facts about Harvoni and Sovaldi

- Harvoni (ledipasvir and sofosbuvir) is a combination of two antiviral drugs that prevent hepatitis C virus from multiplying in the body and is used to treat chronic hepatitis C genotype 1 infection in adults.
- Sovaldi (sofosbuvir) is an antiviral drug that prevents hepatitis C virus from multiplying in the body. Sovaldi should be used together with other hepatitis C drugs. Sovaldi should not be used alone to treat hepatitis C infection.
- Before taking Harvoni or Sovaldi, patients should tell their health care professional if they:
 - have liver problems other than hepatitis, or if they have had a liver transplant
 - have kidney disease, or are on dialysis
 - have human immunodeficiency virus
- Other medicines may affect how Harvoni or Sovaldi work, including prescription and over-the-counter medicines, vitamins, and herbal supplements such as St. John’s wort (*Hypericum perforatum*).

Additional Information for Patients

- We have received reports of an abnormal slowing of the heart rate (bradycardia) when amiodarone is taken together with either the hepatitis C drug Harvoni (ledipasvir/sofosbuvir) or Sovaldi (sofosbuvir) combined with another hepatitis C drug, such as daclatasvir, an investigational direct acting antiviral, or Olysio (simeprevir). Amiodarone is an antiarrhythmic drug and is prescribed to treat an irregular heartbeat.
- Discuss with your health care professional any questions or concerns about your hepatitis C treatment if you are also taking amiodarone. Your health care professional will determine the treatment plan that is most appropriate for you.

- Do not stop taking any of your medicines without first talking to your health care professional even if you have signs and symptoms that might suggest symptomatic bradycardia, a slow heart rate.
- Seek medical attention right away if signs and symptoms of bradycardia are present, such as:
 - Near-fainting or fainting
 - Dizziness or lightheadedness
 - Malaise
 - Weakness
 - Excessive tiredness
 - Shortness of breath
 - Chest pains
 - Confusion or memory problems
- Other medicines may affect how Harvoni or Sovaldi work. Tell your health care professional about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements such as St. John's wort (*Hypericum perforatum*).
- Read the patient information leaflet you get along with each prescription you receive for hepatitis C drugs and amiodarone as there may be new information.
- Report any side effects from the combined use of your hepatitis C drugs with amiodarone to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Additional Information for Health Care Professionals

- Postmarketing cases of serious and life-threatening symptomatic bradycardia, as well as one fatal cardiac arrest and cases requiring pacemaker insertion, have been reported when amiodarone is given with either Harvoni (a fixed dose combination with ledipasvir/sofosbuvir) or Sovaldi (sofosbuvir) combined with another hepatitis C drug, such as daclatasvir, an investigational direct acting antiviral, or Olysio (simeprevir). Bradycardia may occur within the first few hours to days of initiating hepatitis C treatment, but cases have been observed up to 2 weeks after initiating treatment.
- The mechanism for this bradycardia effect is unknown.
- Harvoni should not be coadministered with amiodarone.
- Sovaldi (sofosbuvir) combined with another hepatitis C drug, such as investigational drug daclatasvir or Olysio (simeprevir), should not be coadministered with amiodarone.
- Similar cases of symptomatic bradycardia have not been reported in patients receiving Sovaldi with ribavirin or with pegylated interferon and ribavirin.
- Tell your patients to seek medical attention immediately if they have signs and symptoms of symptomatic bradycardia including:
 - Near-fainting or fainting (syncope)
 - Dizziness or lightheadedness
 - Malaise
 - Weakness
 - Excessive tiredness

- Shortness of breath
 - Chest pains
 - Confusion or memory problems
- For patients taking amiodarone who have no other alternative treatment options and who will be co-administered either Harvoni or Sovaldi in combination with another direct-acting antiviral:
 - Counsel patients about the risk of serious symptomatic bradycardia
 - Cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate would occur on a daily basis through at least the first 2 weeks of treatment
- Patients who are taking either Harvoni or Sovaldi in combination with another direct-acting antiviral, who need to start amiodarone therapy due to no other alternative treatment options, should undergo similar cardiac monitoring as outlined above.
- Due to the long half-life of amiodarone, patients discontinuing amiodarone just prior to starting Harvoni, or Sovaldi in combination with another direct-acting antiviral, should also undergo similar cardiac monitoring as outlined above.
- Encourage patients to read the patient information leaflet they receive with their prescription hepatitis C drugs and amiodarone as there may be new information.
- Report adverse events involving the co-administration of hepatitis C drugs with amiodarone to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

Data Summary

FDA reviewed post-marketing reports of bradycardia submitted by the manufacturer Gilead Sciences and from the FDA Adverse Event Reporting System (FAERS) database. Reports included the use of amiodarone with either Harvoni (ledipasvir/sofosbuvir) or Sovaldi (sofosbuvir) in combination with other direct-acting antivirals, such as investigational drug daclatasvir or Olysio (simeprevir). Based on the reports, the concomitant administration of amiodarone with Harvoni, or with Sovaldi in combination with another direct-acting antiviral, may result in a severe or life-threatening bradycardia.

The postmarketing reports of serious symptomatic bradycardia are difficult to interpret because they occurred in patients with underlying cardiac disease, concomitant beta blocker therapy, and/or advanced liver disease. However, the following characteristics of these postmarketing cases suggest a causal association:

- Short time to symptom onset from starting either Harvoni or Sovaldi in combination with other direct-acting antivirals;
- Resolution of symptoms upon dechallenge;
- Recurrence of symptoms upon rechallenge.

The mechanism of these events due to the coadministration of amiodarone with either Harvoni or with Sovaldi in combination with another direct-acting antiviral is unknown.

Nine patients receiving amiodarone reported symptomatic bradycardia during treatment with either Harvoni or with Sovaldi in combination with another direct-acting antiviral, such as daclatasvir, an investigational direct acting antiviral, or Olysio (simeprevir). Seven of the 9 patients were also receiving a beta blocker.

Six of the 9 patients experienced symptomatic bradycardia within the first 24 hours, and the remaining 3 patients experienced it within the first 2 to 12 days following hepatitis C treatment initiation. One patient had a fatal outcome due to cardiac arrest, and 3 patients required pacemaker intervention.

In 3 of the patients, rechallenge with hepatitis C treatment in the setting of continued amiodarone therapy resulted in recurrence of symptomatic bradycardia. In one patient, discontinuation of amiodarone followed by rechallenge with hepatitis C treatment after 8 weeks did not result in recurrent bradycardia.