

3/20/2015

## IMPORTANT DRUG WARNING

**Subject: Serious and Life-Threatening Cases of Symptomatic Bradycardia as well as One Case of Fatal Cardiac Arrest Reported with Coadministration of Amiodarone With Either Harvoni<sup>®</sup> (ledipasvir and sofosbuvir fixed-dose combination) or With Sovaldi<sup>®</sup> (sofosbuvir) in Combination with Another Direct Acting Antiviral.**

Dear Health Care Provider,

The purpose of this letter is to inform you of new important safety information for Harvoni and Sovaldi.

- Harvoni is indicated for the treatment of chronic hepatitis C genotype 1 infection in adults.
- Sovaldi is indicated for the treatment of chronic hepatitis C infection as a component of a combination antiviral treatment regimen.

### **Serious Risk of Symptomatic Bradycardia With Co-Use of Amiodarone with Either Harvoni or With Sovaldi in Combination with Another Direct Acting Antiviral (DAA)**

- Postmarketing cases of symptomatic bradycardia, as well as one fatal cardiac arrest and cases requiring pacemaker insertion, have been reported in patients taking amiodarone and Harvoni, or amiodarone and Sovaldi in combination with another DAA.
- Bradycardia was observed within hours to days of starting Harvoni, or Sovaldi in combination with another DAA, but cases have been observed up to 2 weeks after initiating HCV treatment.
- Risk factors for the development of symptomatic bradycardia in patients receiving amiodarone may include coadministration of a beta blocker, or those with underlying cardiac comorbidities and/or advanced liver disease.
- Similar cases have not been reported in patients receiving Sovaldi with ribavirin or with pegylated interferon and ribavirin.

### **Warning and Precaution**

Coadministration of amiodarone with either Harvoni or with Sovaldi in combination with another DAA is not recommended.

### **Further Information**

Nine cases of symptomatic bradycardia have been reported during postmarketing in patients receiving amiodarone with either Harvoni, or Sovaldi in combination with another DAA (daclatasvir, an investigational DAA, or Olysio (simeprevir)). Seven patients were also receiving a beta blocker.

- Six cases occurred within the first 24 hours and the remaining 3 cases occurred within the first 2-12 days following HCV treatment initiation.
- One case was a fatal cardiac arrest and 3 cases required pacemaker intervention.
- In 3 cases, rechallenge with HCV treatment in the setting of continued amiodarone therapy resulted in recurrence of symptomatic bradycardia.

- In one case discontinuation of amiodarone followed by rechallenge of HCV treatment after 8 weeks did not result in recurrent bradycardia.
- Three of the 9 cases were in patients receiving Harvoni, 5 cases were in patients receiving Sovaldi plus an investigational agent (daclatasvir) and 1 case was in a patient receiving Sovaldi with Olysio (simeprevir).

The mechanism of the potential interaction between amiodarone and Harvoni, or Sovaldi in combination with another DAA is unknown.

Because the number of patients taking amiodarone who have been exposed to Harvoni or Sovaldi in combination with another DAA is unknown, it is not possible to estimate the incidence of occurrence of these events.

### **Prescriber Action**

For patients taking amiodarone who have no other alternative, viable treatment options and who will be co-administered Harvoni, or Sovaldi in combination with another DAA:

- 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 should occur on a daily basis through at least the first 2 weeks of treatment.

Patients who are taking Harvoni or Sovaldi in combination with another DAA who need to start amiodarone therapy due to no other alternative, viable treatment options should undergo similar cardiac monitoring as outlined above.

Due to amiodarone's long half-life, patients discontinuing amiodarone just prior to starting Harvoni or Sovaldi in combination with a DAA should also undergo similar cardiac monitoring as outlined above.

Tell your patients if they develop signs or symptoms that might suggest symptomatic bradycardia they should seek medical evaluation immediately. Symptoms may include:

- |                                |                                |
|--------------------------------|--------------------------------|
| • Near-fainting or fainting    | • Excessive tiredness          |
| • Dizziness or lightheadedness | • Shortness of breath          |
| • Malaise                      | • Chest pains                  |
| • Weakness                     | • Confusion or memory problems |

Patients should not stop taking any of their medicines without talking to their healthcare provider.

This information is based on currently available data and recommendations may change. Additionally, the product labeling will be updated.

### **Reporting Adverse Events**

Please report all adverse events, following or coincident with the use of Harvoni or Sovaldi, to Gilead Global Drug Safety at 1-800-GILEAD-5, option 3; or to FDA's MedWatch program by telephone at 1-800-332-1088; by fax at 1-800-332-0178; via [www.FDA.gov/medwatch](http://www.FDA.gov/medwatch); or by mail to MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857 (use postage-paid FDA Form 3500).

Please refer to the accompanying full prescribing information and approved patient information for a complete description of the risk profile for Harvoni or Sovaldi.

Contact Gilead Medical Information at 1-800-GILEAD-5, option 2 if you have additional questions.

This information is being sent in agreement with the FDA.

Sincerely,

A handwritten signature in black ink, appearing to read "John McHutchison". The signature is written in a cursive style with a large initial "J" and "M".

John McHutchison, MD  
Executive Vice President, Clinical Research  
Gilead Sciences, Inc.