



NATIONAL PBM BULLETIN

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DEPARTMENT OF VETERANS AFFAIRS VETERANS HEALTH ADMINISTRATION (VHA) PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), AND CENTER FOR MEDICATION SAFETY (VA MEDSAFE)

AMIODARONE USE WITH LEDIPASVIR/SOFOSBUVIR (HARVONI) OR SOFOSBUVIR (SOVALDI) IN COMBINATION WITH ANOTHER DIRECT-ACTING ANTIVIRAL MAY CAUSE BRADYCARDIA

I. ISSUE

FDA warns of serious symptomatic bradycardia when amiodarone is taken with ledipasvir/sofosbuvir (Harvoni) or with sofosbuvir (Sovaldi) taken in combination with another direct acting antiviral for hepatitis C (e.g., simeprevir).

II. BACKGROUND

Ledipasvir/sofosbuvir (Harvoni) and sofosbuvir (Sovaldi) are indicated for the treatment of chronic hepatitis C infection in adults. Based on FDA's review the cause of the bradycardia cannot be determined. "Information about the risk of bradycardia will be added to the Warnings and Precautions, Drug Interactions, and Postmarketing Experience sections of Harvoni and Sovaldi drug labels." FDA will continue to monitor for symptomatic bradycardia and further investigate the cause of bradycardia when using amiodarone and the hepatitis C drugs in combination.

III. DISCUSSION

FDA has reviewed postmarketing adverse event reports from the manufacturer Gilead Sciences and the FDA Adverse Event Reporting System (FAERS) database. The FDA has found that patients taking amiodarone with either ledipasvir/sofosbuvir (Harvoni) or sofosbuvir (Sovaldi) combined with another direct-acting antiviral can develop serious and life-threatening symptomatic bradycardia. The reports included the death of one patient due to cardiac arrest; three patients required a pacemaker. Other patients recovered after discontinuing amiodarone, the hepatitis C drugs, or both. Bradycardia can occur for up to two weeks following combined use of these agents.

IV. PROVIDER RECOMMENDATIONS

- Advise your patients who are taking the drug combination 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.
- Use of ledipasvir/sofosbuvir (Harvoni) or sofosbuvir (Sovaldi) combined with another direct-acting antiviral drug in patients already taking amiodarone is not recommended.
- 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.
 - Since amiodarone has a long half-life, important drug interactions may occur for some time after discontinuation.
- Patients taking ledipasvir/sofosbuvir (Harvoni) or sofosbuvir (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.

Providers should continue to report any adverse reactions with the use of amiodarone, ledipasvir/sofosbuvir (Harvoni), or sofosbuvir (Sovaldi) by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA-0178, online at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>, or by mail).

V. REFERENCES

FDA Drug Safety Communications: 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. <http://www.fda.gov/Drugs/DrugSafety/ucm439484.htm> . (Accessed 3/25/2015).

ACTIONS

- **Facility Director** (or physician designee): Forward this document to the Facility Chief of Staff (COS).
- **Facility COS and Chief Nurse Executives**: Forward this document to all appropriate providers who prescribe these medications (e.g., primary care providers, hepatology, cardiology, including contract providers, etc.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.
- **ACOS for R&D**: Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).