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EMA recommends avoidance of certain hepatitis C medicines and amiodarone together

Concomitant use may increase risk of slow heart rate and related problems

EMA has confirmed a risk of severe bradycardia (slow heart rate) or heart block (problems with conduction of electrical signals in the heart) when the hepatitis C medicines Harvoni (sofosbuvir with ledipasvir) or a combination of Sovaldi (sofosbuvir) and Daklinza (daclatasvir) are used in patients who are also taking the medicine amiodarone, which is an antiarrhythmic (a medicine used to treat irregular heartbeat).

To manage this risk the Agency recommends that amiodarone should only be used in patients taking these hepatitis C medicines if other antiarrhythmics cannot be given. If concomitant use with amiodarone cannot be avoided, patients should be closely monitored. Because amiodarone persists for a long time in the body, monitoring is also needed if patients start such hepatitis C treatments within a few months of stopping amiodarone.

The recommendations follow a review[1] of cases of severe bradycardia or heart block in patients taking amiodarone who started treatment with the hepatitis C combinations. It was considered that there was a likely relationship of these events to the medicines. The possible mechanism behind these effects is unknown and further investigation of other cases with Sovaldi and other hepatitis C medicines is ongoing.

Information for patients

- A few cases of severe slow heart rate or interference with electrical signals in the heart have been reported in patients taking the medicines Harvoni or Sovaldi plus Daklinza (used to treat hepatitis C, a liver infection) at the same time as the heart medicine amiodarone.
- Most of these cases occurred within 24 hours of starting the hepatitis C medicine but some occurred after up to 12 days. Two of the patients needed treatment with a pacemaker and one patient died.

[1] The review was in the context of a "safety signal". A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. The presence of a safety signal does not necessarily mean that a medicine has caused the reported adverse event.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

- Patients who need these hepatitis C combinations should not also be given amiodarone unless there is no other suitable alternative.
- If there is no alternative to giving amiodarone at the same time as the hepatitis C medicine, patients' heart function must be carefully monitored by the doctor. This may include monitoring in hospital for 48 hours after starting treatment.
- Because amiodarone remains in the body for a long time, monitoring is also needed when the hepatitis C treatment is given to patients who stopped amiodarone treatment within the last few months.
- Patients who are taking Harvoni or Sovaldi and Daklinza at the same time as amiodarone, with or without other heart medicines, and who experience symptoms such as slow heartbeat, dizziness, faintness, unusual tiredness, shortness of breath or chest pain during treatment should contact their doctor immediately.
- Patients who have any concerns about their treatment should discuss them with their doctor or pharmacist.

Information for healthcare professionals

- Severe bradycardia and heart block have been reported in patients taking amiodarone and Harvoni, or amiodarone and a combination of Sovaldi and Daklinza. Of 8 cases reviewed up to April 2015, one case resulted in fatal cardiac arrest and two required pacemaker intervention.
- Onset of bradycardia was within 24 hours of initiating hepatitis C treatment in 6 cases and within 2 to 12 days in the other 2 cases. Rechallenge in the context of continued amiodarone treatment resulted in recurrence of symptomatic bradycardia in 2 cases. Recurrence was also seen on rechallenge with the antivirals 8 days after stopping amiodarone, but not 8 weeks after stopping.
- Amiodarone should only be initiated in patients treated with Harvoni, or Sovaldi plus Daklinza, if other antiarrhythmics are contra-indicated or not tolerated.
- If concomitant use with amiodarone is unavoidable, patients should be closely monitored, particularly during the first weeks of treatment. Those at high risk of bradyarrhythmia should be monitored in an appropriate clinical setting for 48 hours after starting concomitant treatment.
- Due to its long half-life, patients who have discontinued amiodarone within the past few months should also be monitored when starting hepatitis C treatment with Harvoni or Sovaldi plus Daklinza.
- Patients receiving these hepatitis C medicines with amiodarone, with or without other medicines that lower heart rate, should be warned of the symptoms of bradycardia and heart block and should be advised to seek urgent medical advice if they experience them.

The product information for Harvoni, Sovaldi and Daklinza will be updated appropriately. A letter will also be sent to healthcare professionals involved in hepatitis C treatment explaining these risks and the measures to manage them.

Because the number of patients taking amiodarone who have been exposed to Harvoni or Sovaldi in combination with Daklinza is unknown, it is not possible to estimate the incidence of occurrence of these events. The mechanism behind the findings has not been established.

More about the medicine

Harvoni, Sovaldi and Daklinza are among several novel hepatitis C treatments recently evaluated by EMA, which are available as tablets. They have simplified the management of the disease and allow the prospect of curing the infection. Sovaldi (sofosbuvir) was authorised in the EU in January 2014, Daklinza (dataclasvir) in August 2014 and Harvoni (sofosbuvir/ledipasvir) in November 2014.

The active substance sofosbuvir blocks the action of an enzyme called 'NS5B RNA-dependent RNA polymerase', while dataclasvir and ledipasvir target a protein called 'NS5A'; by blocking these targets the medicines stop the hepatitis C virus from multiplying and infecting new cells.

Contact our press officer

Monika Benstetter

Tel. +44 (0)20 3660 8427

E-mail: press@ema.europa.eu