



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee

## PRAC recommendations on signals for update of the product information

Adopted at the 7-10 April 2015 PRAC

### 1. Daclatasvir; sofosbuvir; sofosbuvir, ledipasvir – Arrhythmia (EPITT no 18177)

The PRAC has assessed cases of severe arrhythmia associated with the use of sofosbuvir (including in combination with ledipasvir) and/or daclatasvir, in particular in patients with established cardiac disorders and treated with bradycardic medications. The PRAC has noted that amiodarone was involved in cases with the most suggestive causal relationship.

Consequently, the PRAC has agreed the following:

- The MAHs of Sovaldi, Harvoni and Daklinza should submit a variation within 1 month, to amend the product information as described below (<new text underlined / text to be removed with ~~strikethrough~~>)
- The MAHs should distribute a direct healthcare professional communication (DHPC) according to the text and communication plan agreed with the PRAC and CHMP
- The MAHs should closely monitor all cardiac events with and without the concomitant use of amiodarone, beta-blocking agents and other antiarrhythmic agents and present updates of the cumulative safety reviews in the next PSURs. The long half-life of amiodarone should be considered when deciding on cases for reviews
- Taking into account that the mechanism for the drug-drug interaction with amiodarone remains unclear, the MAHs should ensure that planned non-clinical studies investigate both the potential pharmacodynamic and pharmacokinetic effects.

#### Summary of Product Characteristics for Sovaldi, Harvoni, Daklinza

Section 4.4 - Special warnings and precautions for use

Severe Bradycardia and Heart Block



Cases of severe bradycardia and heart block have been observed when <brand name> is used in combination with <adapt according to the product> and concomitant amiodarone with or without other drugs that lower heart rate. The mechanism is not established.

The concomitant use of amiodarone was limited through the clinical development of sofosbuvir plus direct-acting antivirals (DAAs). Cases are potentially life threatening, therefore amiodarone should only be used in patients on <brand name> when other alternative anti-arrhythmic treatments are not tolerated or are contraindicated.

Should concomitant use of amiodarone be considered necessary it is recommended that patients are closely monitored when initiating <brand name>. Patients who are identified as being high risk of bradyarrhythmia should be continuously monitored for 48 hours in an appropriate clinical setting.

Due to the long half-life of amiodarone, appropriate monitoring should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on <adapt according to the product>.

All patients receiving <brand name> in combination with amiodarone with or without other drugs that lower heart rate should also be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them.

#### Section 4.5 - Interaction with other medicinal products and other forms of interaction

<b><u>Amiodarone</u></b>	<u>Interaction not studied.</u>	<u>Use only if no other alternative if available. Close monitoring is recommended if this medicinal product is administered with &lt;brand name&gt; (see sections 4.4 and 4.8).</u>
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#### Section 4.8 - Undesirable effects

Description of selected adverse reactions

##### Cardiac arrhythmias

Cases of severe bradycardia and heart block have been observed when <brand name> is used in combination with <adapt according to the product> and concomitant amiodarone and/or other drugs that lower heart rate (see sections 4.4 and 4.5).

#### **Only Summary of Products Characteristics for Daklinza**

#### Section 4.5 - Interaction with other medicinal products and other forms of interaction

No clinically relevant effects on the pharmacokinetics of either medicinal product are expected when daclatasvir is coadministered with any of the following: PDE-5 inhibitors, medicinal products in the ACE inhibitor class (e.g. enalapril), medicinal products in the angiotensin II receptor antagonist class (e.g. losartan, irbesartan, olmesartan, candesartan, valsartan), ~~amiodarone~~, disopyramide, propafenone, flecainide, mexilitine, quinidine or antacids.

## Package Leaflet for Sovaldi, Harvoni, Daklinza

### Section 2 - What you need to know before you take <brand name>

#### Warnings and precautions

Talk to your doctor or pharmacist before taking <brand name>

- you currently take, or have taken in the last few months, the medicine amiodarone to treat irregular heartbeats (your doctor may consider alternative treatments if have taken this medicine)

Tell your doctor immediately if you are taking any medicines for heart problems and during treatment you experience:

- Shortness of breath
- Light-headedness
- Palpitations
- Fainting

#### Other medicines and <brand name>

Tell your doctor if you take any of the following medicines:

- amiodarone, used to treat irregular heart beats

## 2. Interferon alfa-2a; interferon alfa-2b; interferon beta-1a; interferon beta-1b; peginterferon alfa-2a; peginterferon alfa-2b; peginterferon beta-1a – Pulmonary arterial hypertension (EPITT no 18059)

Based on published clinical and non-clinical data and on spontaneous reports, the PRAC considers that a causal relationship between the use of interferons alfa and beta and the development of pulmonary arterial hypertension, a rare but severe event, cannot be excluded. Therefore the PRAC has agreed that the marketing authorisation holders (MAHs) of interferon alfa and beta containing products should submit a variation within 2 months to amend the product information as described below (new text underlined):

### Summary of Product Characteristics:

#### Section 4.8 - Undesirable effects

*[Interferon alfa and beta containing products]*

“Pulmonary arterial hypertension\*” should be added under the System Organ Class (SOC)

“Respiratory, thoracic and mediastinal disorders” with the frequency “not known”.

“\*Class label for interferon products, see below Pulmonary arterial hypertension.”

#### Section 4.8c

#### Pulmonary arterial hypertension

*[Interferon alfa-containing products]*

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa products, notably in patients with risk factors for PAH (such as portal hypertension, HIV infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alfa.

*[Interferon beta-containing products]*

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products. Events were reported at various time points including up to several years after starting treatment with interferon beta.

#### **Package Leaflet:**

Section 4 - Possible side effects

*[Interferon alfa-containing products]*

Add under frequency not known (frequency cannot be estimated from the available data)

Pulmonary arterial hypertension - a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. This may occur in particular in patients with risk factors such as HIV infection or severe liver problems (cirrhosis). The side effect may develop at various time points during treatment, typically several months after starting treatment with {X}.

*[Interferon beta-containing products]*

Add under frequency not known (frequency cannot be estimated from the available data)

Pulmonary arterial hypertension – a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with {X}.

### **3. Trabectedin – Capillary leak syndrome (EPITT no 18115)**

In the light of available evidence from case reports in EudraVigilance and from data submitted by the MAH, the PRAC has agreed that there is a reasonable possibility of a causal relationship between capillary leak syndrome and the use of trabectedin. Considering the seriousness of the condition, the PRAC concluded that an update of the product information is warranted. Therefore, the MAH for trabectedin should submit a variation within 2 months, to amend the product information as described below (new text underlined).

#### **Summary of Product Characteristics**

Section 4.8 – Undesirable effects

Frequency 'uncommon': Cases of suspected capillary leak syndrome have been reported with trabectedin.