EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 7-10 April 2015

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 7-10 April 2015 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][1] reference numbers).

PRAC recommendations to provide supplementary information are directly actionable by the concerned marketing authorisation holders (MAHs). PRAC recommendations for regulatory action (e.g. amendment of the product information) are submitted to the Committee for Medicinal Products for Human Use (CHMP) for endorsement when the signal concerns Centrally Authorised Products (CAPs), and to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for information in the case of Nationally Authorised Products (NAPs). Thereafter, MAHs are expected to take action according to the PRAC recommendations.

When appropriate, the PRAC may also recommend the conduct of additional analyses by the Agency or Member States.

MAHs are reminded that in line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, they shall ensure that their product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations published on the European Medicines Agency (EMA) website (currently acting as the EU medicines webportal).

For CAPs, at the time of publication, PRAC recommendations for update of product information have been agreed by the CHMP at their plenary meeting (20-23 April 2015) and corresponding variations will be assessed by the CHMP.

For nationally authorised medicinal products, it is the responsibility of the National Competent Authorities (NCAs) of the Member States to oversee that PRAC recommendations on signals are adhered to.

Variations for CAPs are handled according to established EMA procedures. MAHs are referred to the available guidance. Variations for NAPs (including via mutual recognition and decentralised procedures) are handled at national level in accordance with the provisions of the Member States.

[1] The relevant EPITT reference number should be used in any communication related to a signal.

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The established procedures and timelines for submission of variation applications pertaining to generic medicinal products are to be followed.

For procedural aspects related to the handling of PRAC recommendations on signals (e.g. submission requirements, contact points, etc.) please refer to the Questions and Answers on signal management.

1. Recommendations for update of the product information[2]

1.1. Daclatasvir; sofosbuvir; sofosbuvir, ledipasvir – Arrhythmia

Substance (invented name)	Daclatasvir (Daklinza) (EMEA/H/C/003768) Sofosbuvir (Sovaldi) (EMEA/H/C/002798) Sofosbuvir, ledipasvir (Harvoni) (EMEA/H/C/003850)
Authorisation procedure	Centralised
EPITT No	18177
PRAC rapporteur(s)	Margarida Guimarães (PT)
Date of adoption	10 April 2015

Recommendation

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.

[2] Translations in EU languages of the adopted PRAC recommendations for update of the product information will be made available to MAHs via the EMA website. The translations will be reviewed by National Competent Authorities of the Member States and thereafter published. It is expected that this will occur within 3 weeks of publishing this document. From the May 2015 PRAC onwards, the English text and the translations will be published at the same time.

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

Amiodarone	Interaction not studied.	Use only if no other alternative if available. Close monitoring is recommended if this medicinal product is administered with <brand name> (see sections 4.4 and 4.8).

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

1.2. Interferon alfa-2a; interferon alfa-2b; interferon beta-1a; interferon beta-1b; peginterferon alfa-2a; peginterferon alfa-2b; peginterferon beta-1a – Pulmonary arterial hypertension

Substance (invented name)	Interferon alfa-2a Interferon alfa-2b (IntronA) (EMEA/H/C/000281) Interferon beta-1a (Avonex, Rebif) (EMEA/H/C/000102, EMEA/H/C/000136) Interferon beta-1b (Betaferon, Extavia) (EMEA/H/C/000081, EMEA/H/C/000933) Peginterferon alfa-2a (Pegasys) (EMEA/H/C/000395) Peginterferon alfa-2b (PegIntron, ViraferonPeg) (EMEA/H/C/000280, EMEA/H/C/000329) Peginterferon beta-1a (Plegridy) (EMEA/H/C/002827)
Authorisation procedure	Centralised and non-centralised
EPITT No	18059
PRAC rapporteur(s)	Qun-Ying Yue (SE)
Date of adoption	10 April 2015

Recommendation

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 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}.

1.3. Sodium-containing effervescent, dispersible and soluble medicines – Cardiovascular events

Substance (invented name)	Sodium-containing effervescent, dispersible and soluble medicines
Authorisation procedure	Centralised and Non-centralised
EPITT No	17931
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	10 April 2015

Recommendation

The PRAC recommends that the labelling of medicines should be updated to make the sodium content clearer for patients and health care professionals (HCPs). The PRAC noted that currently the Excipient Guideline and SmPC guideline provide advice about how sodium content should be presented in the SmPC and patient leaflet. However, neither of these guidelines encourages the amount of sodium contained in a medicine to be presented in a way that is meaningful or immediately understandable for patients or HCPs.

A study by George et al (BMJ 2013) showed that high sodium in medicines might increase the risk of cardiovascular disease and in particular hypertension. Whilst the limitations of the study were acknowledged, the association for hypertension was extremely strong (OR 7.18, 95% CI 6.74 to 7.65) and is biologically plausible given the established link between dietary sodium and hypertension. The PRAC considered that this study highlighted that medicines especially effervescent and soluble analgesics can contain high levels of sodium.

Therefore, it was agreed that medicines which contain above a certain threshold should be clearly labelled as being high in sodium. High sodium is considered to be ≥17mmol of sodium from active and/or excipients in the maximum daily dose of a product. This is equivalent to ≥20% of the WHO maximum recommended daily intake for sodium for an adult. Defining this threshold for high sodium in medicines has taken into account both the recommended daily amounts of dietary sodium and the fact that sodium from medicines is in addition to sodium from the diet.

Having considered the available evidence in the literature, the PRAC agreed that the MAHs with formulations that meet the criteria listed below, should submit a variation following the publication of the updated Excipient Guideline, at the subsequent routine regulatory opportunity or within 12 months, whichever is sooner.

Criteria for formulations that warrant update of product information

- ≥ 17mmol sodium in the maximum daily dose and that;
- Are for long term use or regular exposure.

As a general guidance, long term use is to be considered as continuous daily use for > 1 month and regular exposure is to be considered repeated use for more than 2 days every week.

High sodium-containing effervescent and soluble products that are most commonly used to treat short term conditions for example cystitis, cold and flu, diarrhoea and bowel preparations would be generally be excluded by the scope as products like these should ordinarily never need to be used on a long term basis, given that the conditions they treat should always be short lived or self-limiting. However, if the indication and/or posology provides for long term or regular use then they should be considered within scope.

The Excipient Guideline will be updated with the new sodium-labelling requirements. The updated wording should be implemented for active ingredients and excipients and should replace any existing wording based on the current Excipient Guideline.

Summary of Product Characteristics:

Section 4.4

This medicinal product contains <X mg> sodium per dose, equivalent to <Y%> of the WHO recommended maximum daily intake for sodium.

The maximum daily dose of this product is equivalent to <Z%> of the WHO recommended maximum daily intake for sodium.

[Product name] is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

Package Leaflet

Section 2

The maximum recommended daily dose of this medicinal product contains <X mg> sodium (found in table salt). This is equivalent to <Y%> of the adult recommended maximum daily dietary intake for sodium.

Talk to your pharmacist or doctor if you need [product name] on a daily basis for a prolonged period of time, especially if you have been advised to have a low salt diet.

Label

High in sodium – see leaflet for further information.

Annex to the PRAC recommendation

Guidance for industry

Sodium is used in medicines for a number of reasons but is commonly used to aid solubility. Consequently, effervescent and soluble medicines in particular can contain high levels of sodium. High sodium in medicines might be associated with a risk of cardiovascular conditions including hypertension and stroke.

To make it easier for patients and health care professionals (HCPs) to see how much sodium is present in medicines, the labelling of sodium is being updated with a focus on those products considered to have a high sodium content.

This will allow patients and HCPs to make informed choices about medicines in terms of sodium content in the context of their individual cardiovascular risk and the availability of lower sodium formulations.

The threshold for high sodium in medicines is ≥17mmol of sodium in the maximum daily dose. 17mmol of sodium is equivalent to 20% of the WHO recommended maximum daily dietary intake of sodium for an adult. This threshold has been chosen as many people already consume too much sodium in their diet. A medicine providing an additional 20% or more of the daily amount of sodium could therefore have a significant impact, particularly for patients at high cardiovascular risk or those attempting to maintain a low-sodium diet.

Products for which the new sodium labelling updates are required are those that

- contain ≥17mmol of sodium from any source in the maximum daily dose AND
- are used long term (continuous daily use for more than one month) or regular exposure (repeated use for more than two days, every week).

It is anticipated that the majority of the products that meet or exceed the threshold of 17mmol will be effervescent or soluble formulations where sodium has been added as an excipient to aid solubility.

However, the total sodium content should be calculated taking into account all the ingredients in the formulation.

High sodium-containing effervescent and soluble products that are most commonly used to treat short term conditions for example cystitis, cold and flu, diarrhoea and bowel preparations would be generally be excluded by the scope, as products like these should ordinarily never need to be used on a long term basis, given that the conditions they treat should always be short lived or self-limiting. However, if the indication and/or posology provides for long term or regular use then they should be considered within scope.

High sodium containing effervescent and soluble analgesics and antacids may be used by patients long-term or regularly as the conditions they are being used to treat may be a chronic problem.

The Excipient Guideline will be updated with the new sodium-labelling requirements.

The updated wording should be implemented for active ingredients and excipients and should replace any existing wording based on the current Excipient Guideline. The labelling requirements for products that contain more than the threshold for sodium will be identical regardless of the source of the sodium (from the active or the excipient).

MAHs should wait for publication of the updated Excipient Guideline and then implement the new wording at the next routine regulatory opportunity or within 12 months, whichever is sooner.

1.4. Trabectedin – Capillary leak syndrome

Substance (invented name)	Trabectedin (Yondelis) (EMEA/H/C/000773)
Authorisation procedure	Centralised
EPITT No	18115
PRAC rapporteur(s)	Torbjörn Callreus (DK)
Date of adoption	10 April 2015

Recommendation

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.

2. Recommendations for submission of supplementary information

The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a **causal relationship** between the medicine and the reported adverse event.

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Clopidogrel	Drug interaction with grapefruit juice leading to potential impairment of therapeutic efficacy (18289)	Margarida Guimarães (PT)	Supplementary information requested (submission by 11/07/2015)	Sanofi
Etanercept	Diarrhoea (18257)	Rafe Suvarna (UK)	Assess in the next PSUR (submission by 13/04/2015)	Pfizer Limited
Leflunomide	Pulmonary hypertension (18221)	Sabine Straus (NL)	Supplementary information requested (submission by 11/07/2015)	Sanofi-aventis Deutschland GmbH
Sildenafil	Non-arteritic anterior ischaemic optic neuropathy (NAION) (18253)	Menno van der Elst (NL)	Assess in the next PSUR (submission by 09/08/2015)	Pfizer Limited
Sitagliptin	Intestinal obstruction (18251)	Menno van der Elst (NL)	Supplementary information requested (submission by 08/08/2015)	Merck Sharp & Dohme Limited
Temsirolimus	Myocardial infarction (18263)	Martin Huber (DE)	Assess in the next PSUR (submission by 29/06/2015)	Pfizer Limited
Vildagliptin	Intestinal obstruction (18251)	Menno van der Elst (NL)	Assess in the next PSUR (submission by 29/05/2015)	Novartis Europharm Ltd

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Hormone replacement therapy medicinal products containing oestrogens or oestrogens and progestogens in combination; Conjugated oestrogens/bazedoxifene	Risk of ovarian cancer (18258)	Menno van der Elst (NL)	No action at this stage	Not applicable
Pantoprazole	Subacute cutaneous lupus erythematosus (18119)	Rafe Suvarna (UK)	Provide comments on proposed product information wording (by 09/05/2015)	Takeda GmbH; AstraZeneca UK Limited; Janssen-Cilag
Ziprasidone	Drug reaction with eosinophilia and systemic symptoms (DRESS) (18222)	Qun-Ying Yue (SE)	No action at this stage (MAHs of ziprasidone-containing generic products expected to align their product information to that of reference product Zeldox/Geodon after completion of ongoing variation)	Not applicable