



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

23 November 2020<sup>1</sup>  
EMA/PRAC/570588/2020 Corr<sup>2</sup>  
Pharmacovigilance Risk Assessment Committee (PRAC)

## PRAC recommendations on signals

Adopted at the 26-29 October 2020 PRAC meeting

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 26-29 October 2020 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT]<sup>3</sup> 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 (9-12 November 2020) 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.

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<sup>1</sup> Expected publication date. The actual publication date can be checked on the webpage dedicated to [PRAC recommendations on safety signals](#).

<sup>2</sup> Change in MAHs concerned for the ceftriaxone signal (see page 3).

<sup>3</sup> The relevant EPITT reference number should be used in any communication related to a signal.



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.

The timeline recommended by PRAC for submission of variations following signal assessment is applicable to both innovator and generic medicinal products, unless otherwise specified.

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<sup>4</sup>

## 1.1. Ceftriaxone – Encephalopathy

<b>Authorisation procedure</b>	Non-centralised
<b>EPITT No</b>	19492
<b>PRAC rapporteur(s)</b>	Zane Neikena (LV)
<b>Date of adoption</b>	29 October 2020

### Recommendation

Upon the available evidence from the non-clinical data, post-marketing setting, clinical trials and literature and taking into account the plausible biological mechanism, the PRAC has agreed that the strength of the causal relationship of encephalopathy with the use of ceftriaxone containing medicinal products is sufficient to add the adverse drug reaction Encephalopathy to the product information of ceftriaxone. The MAHs of ceftriaxone-containing products<sup>5</sup> should submit a variation within 2 months from the publication of the PRAC recommendation to amend the product information as described below (new text underlined):

### Summary of product characteristics

#### 4.4. Special warnings and precautions for use

##### Encephalopathy

Encephalopathy has been reported with the use of ceftriaxone (see section 4.8), particularly in elderly patients with severe renal impairment (see section 4.2) or central nervous system disorders. If ceftriaxone-associated encephalopathy is suspected (e.g. decreased level of consciousness, altered mental state, myoclonus, convulsions), discontinuation of ceftriaxone should be considered.

#### 4.8. Undesirable effects

SOC Nervous system disorders

Frequency 'rare': Encephalopathy

### Package leaflet

#### 2. Warnings and precautions

Talk to your doctor or pharmacist before taking your medicine if:

[...]

- You have liver or kidney problems (see section 4)

#### 4. Possible side effects

Treatment with ceftriaxone, particularly in elderly patients with serious kidney or nervous system problems may rarely cause decreased consciousness, abnormal movements, agitation and convulsions.

<sup>4</sup> Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the [EMA website](#).

<sup>5</sup> All MAHs are concerned, not only the innovator MAH for ceftriaxone (Roche) as stated on the document initially published on 23 November 2020.

## 1.2. Dabrafenib; trametinib – Sarcoidosis

<b>Authorisation procedure</b>	Centralised
<b>EPITT No</b>	19574
<b>PRAC rapporteur(s)</b>	David Olsen (NO)
<b>Date of adoption</b>	29 October 2020

### Recommendation

Having considered the available evidence and following the assessment of the data submitted by the concerned Marketing Authorisation Holder (MAH), the PRAC has agreed that the product information for dabrafenib and trametinib should be updated to reflect the risk of sarcoidosis when the products are used in combination.

If more evidence becomes available in the future, the MAH should consider whether further updates of the product information regarding sarcoidosis are necessary when the products are used in monotherapy.

The MAH of Tafinlar and Mekinist (Novartis Europharm Limited), should submit a variation within two months from the publication of the PRAC recommendation, to amend the product's information as described here (new text underlined):

### Tafinlar (dabrafenib) - Summary of product characteristics

#### 4.4. Special warnings and precautions for use

##### Sarcoidosis

Cases of sarcoidosis have been reported in patients treated with dabrafenib in combination with trametinib, mostly involving the skin, lung, eye and lymph nodes. In the majority of the cases, treatment with dabrafenib and trametinib was maintained. In case of a diagnosis of sarcoidosis, relevant treatment should be considered. It is important not to misinterpret sarcoidosis as disease progression.

#### 4.8. Undesirable effects

Tabulated list of adverse reactions – Table 4

System organ class: Immune system disorders

Uncommon: Sarcoidosis

### Tafinlar (dabrafenib) - Package leaflet

#### 2. What you need to know before you take Tafinlar

Conditions you may need to look out for

An inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes (sarcoidosis). Common symptoms of sarcoidosis may include coughing, shortness of breath, swollen lymph nodes, visual disturbances, fever, fatigue, pain and swelling in the joints and tender bumps on your skin. Tell your doctor if you get any of these symptoms.

#### 4. Possible side effects

Possible side effects when Tafinlar and trametinib are taken together

Uncommon side effects (may affect up to 1 in every 100 people):

- Inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes (sarcoidosis)

### **Mekinist (trametinib) - Summary of product characteristics**

#### 4.4. Special warnings and precautions for use

##### Sarcoidosis

Cases of sarcoidosis have been reported in patients treated with trametinib in combination with dabrafenib, mostly involving the skin, lung, eye and lymph nodes. In the majority of the cases, treatment with trametinib and dabrafenib was maintained. In case of a diagnosis of sarcoidosis, relevant treatment should be considered. It is important not to misinterpret sarcoidosis as disease progression.

#### 4.8. Undesirable effects

Tabulated list of adverse reactions – Table 5

System organ class: Immune system disorders

Uncommon: Sarcoidosis

### **Mekinist (trametinib) - Package leaflet**

#### 2. What you need to know before you take Mekinist

Conditions you need to look out for

An inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes (sarcoidosis). Common symptoms of sarcoidosis may include coughing, shortness of breath, swollen lymph nodes, visual disturbances, fever, fatigue, pain and swelling in the joints and tender bumps on your skin. Tell your doctor if you get any of these symptoms.

#### 4. Possible side effects

Side effects when Mekinist and dabrafenib are taken together

Uncommon side effects (may affect up to 1 in 100 people):

- Inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes (sarcoidosis)

### 1.3. Ibrutinib – Hepatitis E

<b>Authorisation procedure</b>	Centralised
<b>EPITT No</b>	19569
<b>PRAC rapporteur(s)</b>	Nikica Mirošević Skvrce (HR)
<b>Date of adoption</b>	29 October 2020

#### **Recommendation** [see also section 3]

Having considered the available evidence and following the assessment of the data submitted by the concerned Marketing Authorisation Holder (MAH), the PRAC has agreed that the product information for ibrutinib should be updated to reflect the potential risk of hepatitis E.

The MAH of Imbruvica (Janssen-Cilag International NV), should submit a variation within two months from the publication of the PRAC recommendation, to amend the product information as described here (new text underlined):

#### **Summary of product characteristics**

##### 4.4. Special warnings and precautions for use

###### Infections

Infections (including sepsis, neutropenic sepsis, bacterial, viral, or fungal infections) were observed in patients treated with IMBRUVICA. Some of these infections have been associated with hospitalisation and death. Most patients with fatal infections also had neutropenia. Patients should be monitored for fever, abnormal liver function tests, neutropenia and infections and appropriate anti-infective therapy should be instituted as indicated. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

[...]

Cases of hepatitis E, which may be chronic, have occurred in patients treated with IMBRUVICA.

#### **Package leaflet**

##### 2. What you need to know before you take IMBRUVICA

###### Warnings and precautions

You may experience viral, bacterial, or fungal infections during treatment with IMBRUVICA. Contact your doctor if you have fever, chills, weakness, confusion, body aches, cold or flu symptoms, feel tired or feel short of breath, yellowing of the skin or eyes (jaundice). These could be signs of an infection.

## 1.4. Lamotrigine – Photosensitivity

<b>Authorisation procedure</b>	Non-centralised
<b>EPITT No</b>	19548
<b>PRAC rapporteur(s)</b>	Liana Gross-Martirosyan (NL)
<b>Date of adoption</b>	29 October 2020

### Recommendation

Based on the review of the data on the risk of photosensitivity with lamotrigine, the PRAC has agreed that the MAH(s) of lamotrigine-containing medicinal product(s) should submit a variation within 2 months, to amend the product information as described below (new text underlined):

#### Summary of product characteristics

##### 4.4. Special warnings and precautions for use

Skin rash (*new text to be added at the end of the paragraph*)

[...]

There have also been reports of photosensitivity reactions associated with lamotrigine use (see section 4.8). In several cases, the reaction occurred with a high dose (400mg or more), upon dose escalation or rapid up-titration. If lamotrigine-associated photosensitivity is suspected in a patient showing signs of photosensitivity (such as an exaggerated sunburn), treatment discontinuation should be considered. If continued treatment with lamotrigine is considered clinically justified, the patient should be advised to avoid exposure to sunlight and artificial UV light and take protective measures (e.g. use of protective clothing and sunscreens).

##### 4.8. Undesirable effects

System Organ Class	Adverse events	Frequency
[...]		
Skin and subcutaneous tissue disorders	Skin rash <sup>5†§</sup>	Very common
	Alopecia, <u>photosensitivity reaction</u>	Uncommon
	Stevens–Johnson Syndrome <sup>§</sup>	Rare
	Toxic epidermal necrolysis	Very rare
	Drug Reaction with Eosinophilia and Systemic Symptoms	Very rare

### Package leaflet

#### 2. What you need to know before you take [product name]

[...]

Take special care with [product name]

Talk to your doctor or pharmacist before taking [product name]:

- [...]
- if you have ever developed a rash after taking lamotrigine or other medicines for bipolar disorder or epilepsy; or if you experience a rash or sunburn after taking lamotrigine and having been exposed to sun or artificial light (e.g. solarium). Your doctor will check your treatment and may advise you to avoid sunlight or protect yourself against the sun (e.g. use of a sunscreen and/or to wear protective clothing).
- [...]

If any of these applies to you:

-> **Tell your doctor**, who may decide to lower the dose, or that [product name] is not suitable for you.

[...]

#### 4. Possible side effects

[...]

Uncommon side effects

These may affect up to 1 in 100 people:

- [...]
- skin rash or sunburn after exposure to sun or artificial light (photosensitivity)

## 2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Anakinra; canakinumab	Drug reaction with eosinophilia and systemic symptoms (DRESS) (19566)	Hans Christian Siersted (DK)	Supplementary information requested (submission by 6 January 2021)	Swedish Orphan Biovitrum AB, Novartis Europharm Limited
Immune checkpoint inhibitors: atezolizumab; avelumab; cemiplimab; durvalumab; ipilimumab; pembrolizumab; nivolumab	Immune-mediated cystitis (19610)	Menno van der Elst (NL)	Supplementary information requested (submission by 6 January 2021)	Merck Sharp & Dohme B.V., Bristol-Myers Squibb Pharma EEIG, Roche Registration GmbH, Merck Europe B.V., AstraZeneca AB, Regeneron Ireland U.C.

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Trastuzumab emtansine	Extravasation and epidermal necrosis (19611)	Hans Christian Siersted (DK)	Supplementary information requested (submission by 6 January 2021)	Roche Registration GmbH

### 3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Cannabidiol; calcineurin inhibitors (tacrolimus, ciclosporin); mammalian Target Of Rapamycin (mTOR) inhibitors (everolimus, sirolimus, temsirolimus)	Drug interaction with cannabidiol leading to calcineurin inhibitors and mTOR inhibitors plasma concentrations increase and toxicity (19614)  EMA Signal Management Lead: Gilles Touraille (Gilles.Touraille@ema.europa.eu)	Rhea Fitzgerald (IE)	No action resulting from the signal procedure for Epidyolex	GW Pharma (International) B.V. (MAH of Epidyolex)
			Product information update (SmPC section 4.5 and package leaflet) with the same wording as the one to be adopted in an ongoing procedure for Epidyolex (EMA/H/C/004675/II/0005).  Concerned MAHs should monitor the Epidyolex product information for the wording update regarding the risk of interaction with calcineurin inhibitors and mTOR inhibitors. A variation application should be submitted within 60 days of its publication.	MAHs of medicinal products for systemic use containing calcineurin inhibitors (tacrolimus, ciclosporin) or mTOR inhibitors (everolimus, sirolimus, temsirolimus)
Cefepime	Drug reaction with eosinophilia and systemic symptoms (DRESS) (17866)	Ana Sofia Martins (PT)	Monitor DRESS and provide a cumulative review of DRESS cases in the upcoming PSUR	MAHs of cefepime-containing products
			Discuss new cases of DRESS within the upcoming PSUR	Bristol-Myers Squibb

<b>INN</b>	<b>Signal (EPITT No)</b>	<b>PRAC Rapporteur</b>	<b>Action for MAH</b>	<b>MAH</b>
Ibrutinib	Hepatitis E (19569)	Nikica Mirošević Skvrce (HR)	<ul style="list-style-type: none"> <li>· See section 1.3</li> <li>· Review hepatotoxicity in the PSUR (submission by 21 January 2021)</li> </ul>	Janssen-Cilag International NV
Immune checkpoint inhibitors: atezolizumab; avelumab; cemiplimab; durvalumab; ipilimumab; nivolumab; pembrolizumab	Eosinophilic fasciitis (19567)	Brigitte Keller-Stanislawski (DE)	Routine pharmacovigilance	Merck Sharp & Dohme B.V., Bristol-Myers Squibb Pharma EEIG, Roche Registration GmbH, Merck Europe B.V., AstraZeneca AB, Regeneron Ireland U.C.