



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

## PRAC recommendations on signals

Adopted at the 25-29 September 2017 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 25-29 September 2017 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT]<sup>1</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 October 2017) 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.

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<sup>1</sup> The relevant EPITT reference number should be used in any communication related to a signal.



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>2</sup>

## 1.1. Acetazolamide – Acute generalised exanthematous pustulosis (AGEP)

Authorisation procedure	Non-centralised
EPI TT No	18892
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of adoption	29 September 2017

### Recommendation

Having considered the available evidence in EudraVigilance and in the literature with regards to the risk of acute generalised exanthematous pustulosis (AGEP) with acetazolamide, the PRAC has agreed that the MAH(s) of acetazolamide-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

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis (AGEP) (see section 4.8). In case of AGEP diagnosis, acetazolamide should be discontinued and any subsequent administration of acetazolamide contraindicated.

##### 4.8. Undesirable effects

Skin and subcutaneous tissue disorders

Not known: acute generalised exanthematous pustulosis (AGEP)

#### Package leaflet

##### 4. Possible side effects

Contact a doctor immediately if you experience a serious skin reaction: a red, scaly rash with bumps under the skin and blisters (exanthematous pustulosis). The frequency of this side effect is not known (cannot be estimated from the available data).

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<sup>2</sup> Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the EMA website.

## 1.2. Azithromycin; clarithromycin; erythromycin; roxithromycin – Acute generalised exanthematous pustulosis (AGEP)

Authorisation procedure	Non-centralised
EPITT No	18891
PRAC rapporteur(s)	Almath Spooner (IE)
Date of adoption	29 September 2017

### Recommendation

Having considered the available evidence in EudraVigilance and in the literature with regards to the risk of acute generalised exanthematous pustulosis (AGEP) with clarithromycin, erythromycin, azithromycin and roxithromycin, the PRAC has agreed that the MAH(s) of clarithromycin, erythromycin, azithromycin and roxithromycin-containing medicinal product(s) should submit a variation within 2 months, to amend the product information as described below (new text underlined):

### Clarithromycin

#### Summary of product characteristics

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

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCAR) (e.g. Acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome, toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms (DRESS)), clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

##### 4.8. Undesirable effects

Skin and subcutaneous tissue disorders

Not known: acute generalised exanthematous pustulosis (AGEP)

#### Package leaflet

##### 4. Possible side effects

Contact a doctor immediately if you experience a serious skin reaction: a red, scaly rash with bumps under the skin and blisters (exanthematous pustulosis). The frequency of this side effect is not known (cannot be estimated from the available data).

### Erythromycin

#### Summary of product characteristics

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

As with other macrolides, rare serious allergic reactions, including acute generalised exanthematous pustulosis (AGEP) have been reported. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the

allergic symptoms may occur when symptomatic therapy is discontinued.

#### 4.8. Undesirable effects

Skin and subcutaneous tissue disorders

Not known: acute generalised exanthematous pustulosis (AGEP)

### **Package leaflet**

#### 4. Possible side effects

Contact a doctor immediately if you experience a serious skin reaction: a red, scaly rash with bumps under the skin and blisters (exanthematous pustulosis). The frequency of this side effect is not known (cannot be estimated from the available data).

### **Azithromycin**

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

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

Hypersensitivity

As with erythromycin and other macrolides, rare serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with <product name> have resulted in recurrent symptoms and required a longer period of observation and treatment.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

#### 4.8. Undesirable effects

Skin and subcutaneous tissue disorders

Rare: acute generalised exanthematous pustulosis (AGEP)

### **Package Leaflet**

#### 4. Possible side effects

Serious skin reactions

Rare: skin eruption that is characterised by the rapid appearance of areas of red skin studded with small pustules (small blisters filled with white/yellow fluid).

## Roxithromycin

### Summary of product characteristics

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

##### Severe bullous reactions

Cases of severe bullous skin reactions such as Stevens Johnson syndrome, toxic epidermal necrolysis and acute generalised exanthematous pustulosis (AGEP), have been reported with roxithromycin. If symptoms or signs of AGEP, SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, roxithromycin treatment should be discontinued.

#### 4.8. Undesirable effects

##### Skin and subcutaneous tissue disorders

Not known: acute generalised exanthematous pustulosis (AGEP)

### Package leaflet

#### 2. What you need to know before you take <product name>

If a widespread, severe skin rash occurs, including skin blistering or peeling, as well as signs of flu and fever (Stevens-Johnson syndrome), a general unwell feeling, fever, chills and muscle aches (toxic epidermal necrolysis), or a red, scaly rash with bumps under the skin and blisters (acute generalised exanthematous pustulosis), refer to a doctor immediately since these skin effects may be life-threatening.

#### 4. Possible side effects

##### Serious skin reactions

Contact a doctor immediately if you experience a serious skin reaction: a red, scaly rash with bumps under the skin and blisters (exanthematous pustulosis). The frequency of this side effect is not known (cannot be estimated from the available data).

### 1.3. Cladribine – Progressive multifocal leukoencephalopathy (PML)

<b>Authorisation procedure</b>	Centralised and non-centralised
<b>EPITT No</b>	18875
<b>PRAC rapporteur(s)</b>	Patrick Batty (UK)
<b>Date of adoption</b>	29 September 2017

#### Recommendation [see also section 3]

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the Marketing Authorisation Holders (MAHs) of cladribine-containing products authorised for oncology indications, should submit a variation within 2 months to amend the product information as described below (new text underlined).

The MAHs should consider Progressive Multifocal Leukoencephalopathy (PML) a potential risk in the Risk Management Plan (RMP) and Periodic Safety Update Reports (PSUR) and follow-up appropriately. There is no need to submit a new RMP for the products with no RMP in place.

Moreover, the MAHs should distribute a Direct Healthcare Professional Communication (DHPC) according to text and communication plan agreed with the CHMP.

#### Summary of product characteristics

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

##### Progressive multifocal leukoencephalopathy (PML)

Cases of PML, including fatal cases, have been reported with cladribine. PML was reported 6 months to several years after treatment with cladribine. An association with prolonged lymphopenia has been reported in several of these cases. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms.

Suggested evaluation for PML includes neurology consultation, magnetic resonance imaging of the brain, and cerebrospinal fluid analysis for JC virus (JCV) DNA by polymerase chain reaction (PCR) or a brain biopsy with testing for JCV. A negative JCV PCR does not exclude PML. Additional follow-up and evaluation may be warranted if no alternative diagnosis can be established. Patients with suspected PML should not receive further treatment with cladribine.

#### Package leaflet

##### 2. What you need to know before you <take> <use> <product name>

##### Warnings and precautions

Talk to your doctor <or> <pharmacist> <or nurse> before <taking> <using> <product name>

At any time during or after your treatment, **tell your doctor or nurse immediately** if you:

experience blurred, loss of or double vision, difficulty speaking, weakness in an arm or a leg, a change in the way you walk or problems with your balance, persistent numbness, decreased sensation or loss

of sensation, memory loss or confusion. These may all be symptoms of a **serious and potentially fatal brain condition** known as progressive multifocal leukoencephalopathy (PML).

If you had these symptoms prior to treatment with cladribine, **tell your doctor** about any change in these symptoms.

#### **1.4. Desloratadine; loratadine – Weight increased in children**

<b>Authorisation procedure</b>	Centralised and non-centralised
<b>EPITT No</b>	18906
<b>PRAC rapporteur(s)</b>	Laurence de Fays (BE)
<b>Date of adoption</b>	29 September 2017

### **Recommendation**

Having considered the available evidence in EudraVigilance and in the literature, and the known role of Histamine H1 receptors in mediating energy intake and expenditure, the PRAC has agreed that the MAHs of loratadine and desloratadine-containing medicinal products should submit a variation within 2 months to amend the product information as described below (new text underlined).

#### **Loratadine**

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

###### 4.8. Undesirable effects

###### Investigations

Frequency 'not known': weight increased

##### **Package leaflet**

###### 4. Possible side effects

Frequency 'not known': weight increased

#### **Desloratadine**

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

###### 4.8. Undesirable effects

###### Investigations

Frequency 'not known': weight increased

###### Metabolism and nutrition disorders

Frequency 'not known': increased appetite

## Package leaflet

### 4. Possible side effects

Frequency 'not known': weight increased, increased appetite

## 1.5. Doxycycline – Doxycycline induced Jarisch-Herxheimer reaction

<b>Authorisation procedure</b>	Non-centralised
<b>EPITT No</b>	18937
<b>PRAC rapporteur(s)</b>	Martin Huber (DE)
<b>Date of adoption</b>	29 September 2017

## Recommendation

Having considered the available evidence in EudraVigilance and in the literature, and the known association of doxycycline with Jarisch-Herxheimer reaction, the PRAC has agreed that the MAHs of doxycycline-containing medicinal products 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

Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction shortly after doxycycline treatment is started. Patients should be reassured that this is a usually self-limiting consequence of antibiotic treatment of spirochete infections.

#### 4.8. Undesirable effects

Immune system disorders

Frequency 'Not known': Jarisch-Herxheimer reaction (see section 4.4)

## Package leaflet

### 4. Possible side effects

If any of the side effects listed below occur, contact your doctor as soon as possible:

- the Jarisch-Herxheimer reaction which causes fever, chills, headache, muscle pain, and skin rash that is usually self-limiting. This occurs shortly after starting doxycycline treatment for infections with spirochete such as Lyme disease.

## 1.6. Flucloxacillin – High anion gap metabolic acidosis (HAGMA)

Authorisation procedure	Non-centralised
EPITT No	18844
PRAC rapporteur(s)	Ana Sofia Diniz Martins (PT)
Date of adoption	29 September 2017

### Recommendation

Having considered the available evidence in EudraVigilance and in the literature with regards to the risk of high anion gap metabolic acidosis when flucloxacillin is used concomitantly with paracetamol, the PRAC has agreed that the MAHs of flucloxacillin-containing medicinal products 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

Caution is advised when flucloxacillin is administered concomitantly with paracetamol due to the increased risk of high anion gap metabolic acidosis (HAGMA). Patients at high risk for HAGMA are in particular those with severe renal impairment, sepsis or malnutrition especially if the maximum daily doses of paracetamol are used.

After co-administration of flucloxacillin and paracetamol, a close monitoring is recommended in order to detect the appearance of acid–base disorders, namely HAGMA, including the search of urinary 5-oxoproline.

If flucloxacillin is continued after cessation of paracetamol, it is advisable to ensure that there are no signals of HAGMA, as there is a possibility of flucloxacillin maintaining the clinical picture of HAGMA (see section 4.5).

#### 4.5. Interaction with other medicinal products and other forms of interaction

Caution should be taken when flucloxacillin is used concomitantly with paracetamol as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risk factors. (see section 4.4.)

#### 4.8. Undesirable effects

##### Metabolism and nutrition disorders

Post marketing experience: very rare cases of high anion gap metabolic acidosis, when flucloxacillin is used concomitantly with paracetamol, generally in the presence of risk factors (see section 4.4.)

### Package leaflet

#### 2. What you need to know before taking <product name>

##### Warnings and precautions

Talk to your doctor or pharmacist before taking this medicine:

- If you are taking or will be taking paracetamol

There is a risk of blood and fluid abnormality (high anion gap metabolic acidosis) which occurs when there is an increase in plasma acidity, when flucloxacillin is used concomitantly with paracetamol, particularly in certain groups of patients at risk, e.g. patients with severe renal impairment, sepsis or malnutrition, especially if the maximum daily doses of paracetamol are used. High anion gap metabolic acidosis is a serious disease that must have urgent treatment.

#### 4. Possible side effects

[The following adverse drug reaction should be added with a frequency very rare (may affect up to 1 in 10,000 people)]

Very rare cases of blood and fluid abnormality (high anion gap metabolic acidosis) which occurs when there is an increase in plasma acidity, when flucloxacillin is used concomitantly with paracetamol, generally in the presence of risk factors (see section 2).

## 2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Apixaban; dabigatran; edoxaban; rivaroxaban	Cholesterol embolisms (19078)	Menno van der Elst (NL)	Supplementary information requested (submission by 6 December 2017)	Boehringer Ingelheim International GmbH; Bristol-Myers Squibb; Daiichi Sankyo Europe GmbH; Bayer AG
Baricitinib	Pneumonia (18950)	Patrick Batty (UK)	Supplementary information requested (submission by 6 December 2017)	Eli Lilly Nederland B.V.
Exenatide	Cardiac arrhythmias (18938)	Qun-Ying Yue (SE)	Assess in currently ongoing PSUSA procedure	AstraZeneca AB
Iloprost	Bradycardia (18935)	Caroline Laborde (FR)	Assess in the next PSUR (submission by 14 December 2017)	Bayer Pharma AG
Teriflunomide	Lymphoma (18960)	Martin Huber (DE)	Assess in the next PSUR (submission by 21 November 2017)	Sanofi-Aventis Groupe

### 3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Cladribine	Progressive multifocal leukoencephalopathy (PML) (18875)	Patrick Batty (UK)	<ul style="list-style-type: none"> <li>• See section 1.3</li> <li>• Update the RMP (no need to submit a new RMP for products with no RMP in place)</li> <li>• Circulate a Direct Healthcare Professional Communication (DHPC)</li> </ul>	MAHs of cladribine-containing products authorised for oncology indications
Gefitinib	Recall phenomenon (18857)	Ulla Wändel-Liminga (SE)	Monitor in PSUR	AstraZeneca AB
Gonadotropin-releasing hormone (GnRH) agonists: buserelin; goserelin; leuprorelin; triptorelin	Thromboembolic events (19084)	Valerie Strassmann (DE)	Routine pharmacovigilance	MAHs of buserelin, goserelin, leuprorelin and triptorelin containing products
Insulin (pre-filled pens and cartridges)	Potential increased risk of medication error associated with withdrawing insulin from pre-filled pens and cartridges, leading to dysglycaemia (18893)	Julie Williams (UK)	No action at this stage	Not applicable