12 October 2017
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Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 25-29 September 2017 PRAC

The product information wording in this document is extracted from the document entitled 'PRAC recommendations on signals' which contains the whole text of the PRAC recommendations for product information update, as well as some general guidance on the handling of signals. It can be found ***here*** (in English only).

New text to be added to the product information is underlined. Current text to be deleted is ~~struck through~~.

1. Acetazolamide – Acute generalised exanthematous pustulosis (AGEP) (EPITT no 18892)

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

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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).

2. Azithromycin; clarithromycin; erythromycin; roxithromycin – Acute generalised exanthematous pustulosis (AGEP) (EPITT no 18891)

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).

3. Cladribine – Progressive multifocal leukoencephalopathy (PML) (EPITT no 18875)

Medicinal products concerned: cladribine-containing products authorised for oncology indications.

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.

4. Desloratadine; loratadine – Weight increased in children (EPITT no 18906)

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

5. Doxycycline – Doxycycline induced Jarisch-Herxheimer reaction (EPITT no 18937)

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.

6. Flucloxacillin – High anion gap metabolic acidosis (HAGMA) (EPITT no 18844)

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, generaly 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, generaly in the presence of risk factors (see section 2).