31 May 2021[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 3-6 May 2021 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. Alemtuzumab – Sarcoidosis (EPITT no 19638)

Summary of product characteristics

4.4. Special warnings and precautions for use

Autoimmunity

[…] Reported autoimmune conditions, include thyroid disorders, immune thrombocytopenic purpura (ITP), nephropathies (e.g. anti-glomerular basement membrane disease), autoimmune hepatitis (AIH), ~~and~~ acquired haemophilia A, and sarcoidosis. […]

[…]

4.8. Undesirable effects

Immune system disorders

Frequency uncommon: Sarcoidosis

Package leaflet

2. What you need to know before you are administered LEMTRADA

[1] Expected publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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[…]

- **Autoimmune conditions**

[…]

o Sarcoidosis
There have been reports of an immune system disorder (sarcoidosis) in patients treated with LEMTRADA. Symptoms can include persistent dry cough, shortness of breath, chest pain, fever, lymph node swelling, weight loss, skin rashes, and blurred vision.

[…]

4. Possible side effects

[…]

The most important side effects are the autoimmune conditions described in section 2 which include:

[…]

- Sarcoidosis (uncommon – may affect up to 1 in 100 people): Symptoms can include persistent dry cough, shortness of breath, chest pain, fever, lymph node swelling, weight loss, skin rashes, and blurred vision.

[…]

These are the **side effects** that you may experience:

Uncommon (may affect up to 1 in 100 people)

- Sarcoidosis
- […]

2. Clindamycin for systemic use – Acute renal failure (EPITT no 19647)

Summary of product characteristics

4.4. Special warnings and precautions for use

Acute kidney injury

Acute kidney injury, including acute renal failure, has been reported infrequently. Therefore, monitoring of renal function should be considered in patients receiving prolonged therapy, suffering from pre-existing renal dysfunction or taking concomitant nephrotoxic drugs (see section 4.8).

4.8. Undesirable effects

Renal and urinary disorders

Frequency 'not known': Acute kidney injury[#]

See section 4.4

Package leaflet

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

Warnings and precautions

Acute kidney disorders may occur. Please inform your doctor about any medication you currently take and if you have any existing problems with your kidneys. If you experience decreased urine output, fluid retention causing swelling in your legs, ankles or feet, shortness of breath, or nausea you should contact your doctor immediately.

4. Possible side effects

Tell your doctor immediately if you develop:

- fluid retention causing swelling in your legs, ankles or feet, shortness of breath or nausea

3. COVID-19 mRNA[2] vaccine (nucleoside-modified) (Comirnaty) – Localised swelling in persons with history of dermal filler injections (EPITT no 19674)

Summary of product characteristics

4.8. Undesirable effects

General disorders and administration site conditions

Not known: Facial swelling*

*Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.

Package leaflet

4. Possible side effects

Not known (cannot be estimated from the available data)

Swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)

4. Secukinumab – Henoch-Schonlein purpura (EPITT no 19640)

Summary of product characteristics

4.8. Undesirable effects

System Organ Class	Frequency	Adverse reaction
Skin and Subcutaneous Tissue Disorders	Rare	Hypersensitivity vasculitis

[2] Messenger ribonucleic acid

Package leaflet

4. Possible side effects

Other side effects

Rare (may affect up to 1 in 1,000 people)

Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps (vasculitis)

5. Sulfamethoxazole, trimethoprim (co-trimoxazole) – Acute respiratory distress syndrome (ARDS) (EPITT no 19625)

The wording applies to all co-trimoxazole containing medicinal products. If there is a reference to lung infiltration or respiratory toxicity already included in section 4.4, the proposed recommendation on ARDS should supersede current wording in place. The same applies for the package leaflet.

Summary of product characteristics

4.4. Special warnings and precautions for use

Respiratory toxicity

Very rare, severe cases of respiratory toxicity, sometimes progressing to Acute Respiratory Distress Syndrome (ARDS), have been reported during co-trimoxazole treatment. The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function may be preliminary signs of ARDS. In such circumstances, co-trimoxazole should be discontinued and appropriate treatment given.

Package leaflet

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

Warnings and precautions

If you develop an unexpected worsening of cough and shortness of breath, inform your doctor immediately.

6. Sulfamethoxazole, trimethoprim (co-trimoxazole) – Haemophagocytic lymphohistiocytosis (EPITT no 19655)

Summary of product characteristics

4.4. Special warnings and precautions for use

Haemophagocytic lymphohistiocytosis (HLH)

Cases of HLH have been reported very rarely in patients treated with co-trimoxazole. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of an excessive systemic inflammation (e.g. fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenias and haemophagocytosis). Patients who develop

early manifestations of pathologic immune activation should be evaluated immediately. If diagnosis of HLH is established, co-trimoxazole treatment should be discontinued.

Package leaflet

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

Warnings and precautions

Haemophagocytic lymphohistiocytosis

There have been very rare reports about excessive immune reactions due to a dysregulated activation of white blood cells resulting in inflammations (haemophagocytic lymphohistiocytosis), which can be life-threatening if not diagnosed and treated early. If you experience multiple symptoms such as fever, swollen glands, feeling weak, lightheaded, shortness of breath, bruising, or skin rash simultaneously or with a slight delay, contact your doctor immediately.

7. Tramadol; tramadol, dexketoprofen; tramadol, paracetamol – Serotonin syndrome (EPITT no 19635)

Due to differences in the national Summaries of Product Characteristics and Package Leaflets, it is acknowledged that further text already included in the product information will have to be modified/adjusted in order to accommodate the new text stated in this PRAC recommendation.

Summary of product characteristics

4.4. Special warnings and precautions for use

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone (see sections 4.5, 4.8 and 4.9).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations.

Symptoms of serotonin syndrome may include mental status changes, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms. Withdrawal of the serotonergic drugs usually brings about a rapid improvement.

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

Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonin ~~toxicity~~ syndrome, a potentially life-threatening condition (see sections 4.4 and 4.8). ~~Serotonin syndrome is likely when one of the following is observed:~~

~~• Spontaneous clonus~~

~~• Inducible or ocular clonus with agitation or diaphoresis~~

~~• Tremor and hyperreflexia~~

~~• Hypertonia and body temperature > 38 °C and inducible or ocular clonus~~

~~Withdrawal of the serotonergic drugs usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.~~

4.8. Undesirable effects

Nervous system disorders

Not known: Serotonin syndrome

4.9. Overdose

Serotonin syndrome has also been reported.

Package leaflet

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

Warnings and precautions

Talk to your doctor before taking <product name> if you:

Suffer from depression and you are taking antidepressants as some of them may interact with tramadol (see 'Other medicines and <product name>').

[…]

There is a small risk that you may experience a so-called serotonin syndrome that can occur after having taken tramadol in combination with certain antidepressants or tramadol alone. Seek medical advice immediately if you have any of the symptoms related to this serious syndrome (see section 4 'Possible side effects').

Other medicines and <product name>

[…]

The risk of side effects increases,

[..]

- if you are taking certain antidepressants, <product name> may interact with these medicines and you may experience serotonin syndrome (see section 4 'Possible side effects'). ~~symptoms such as involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye, agitation, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38°C~~.

4. Possible side effects

Not known: frequency cannot be estimated from the available data

Serotonin syndrome, that can manifest as mental status changes (e.g. agitation, hallucinations, coma), and other effects, such as fever, increase in heart rate, unstable blood pressure, involuntary twitching, muscular rigidity, lack of coordination and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) (see section 2 'What you need to know before you take <product name>').