6 May 2024[1]
EMA/PRAC/147680/2024
Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 8-11 April 2024 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 on the webpage for PRAC recommendations on safety signals (in English only).

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

1. Adagrasib – Serious cutaneous adverse reactions (SCARs) (EPITT no 20051)

Summary of product characteristics

4.4 Special warnings and precautions for use

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with Krazati.

Patients should be advised of the signs and symptoms and be monitored closely for skin reactions. If a SCAR is suspected, Krazati should be withheld, and the patient should be referred to a specialised unit for assessment and treatment. If SJS, TEN or DRESS related to adagrasib is confirmed, Krazati should be permanently discontinued.

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

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Package leaflet

2. Warnings and precautions

Serious and potentially fatal skin reactions (such as Stevens–Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms) have been reported in association with Krazati.

Stop using Krazati and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions (which may include reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes, widespread rash, and enlarged lymph nodes. These serious skin rashes can be preceded by fever and flu-like symptoms).

2. Atezolizumab; avelumab; cemiplimab; dostarlimab; durvalumab; ipilimumab; nivolumab; nivolumab, relatlimab; pembrolizumab; tislelizumab; tremelimumab – Coeliac disease (EPITT no 19958)

Pembrolizumab

Summary of product characteristics

4.8 Undesirable effects

Table 2: Adverse reactions in patients treated with pembrolizumab

	Monotherapy	**In combination with chemotherapy**	**In combination with axitinib or lenvatinib**
Gastrointestinal disorders			
Rare	small intestinal perforation, coeliac disease	small intestinal perforation, coeliac disease	small intestinal perforation
Not known			coeliac disease

Package leaflet

4. Possible side effects

The following side effects have been reported with pembrolizumab alone:

Rare (may affect up to 1 in 1000 people)

- Coeliac disease (characterized by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

The following side effects have been reported in clinical studies with pembrolizumab in combination with chemotherapy:

Rare (may affect up to 1 in 1000 people)

- Coeliac disease (characterized by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

The following side effects have been reported in clinical studies with pembrolizumab in combination with axitinib or lenvatinib:

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):

- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Ipilumumab

Summary of product characteristics

4.8 Undesirable effects

Table 4: Adverse reactions in patients with advanced melanoma treated with ipilimumab 3 mg/kg

Gastrointestinal disorders	
Rare	coeliac disease

Table 5: Adverse reactions with ipilimumab in combination with other therapeutic agents

	Combination with nivolumab (with or without chemotherapy)
Gastrointestinal disorders	
Rare	coeliac disease

Package leaflet

4 Possible side effects

The following side effects have been reported in patients receiving 3 mg/kg ipilimumab alone:

Rare (may affect up to 1 in 1000 people)

- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

The following side effects have been reported with ipilimumab in combination with other anti-cancer medicines (the frequency and severity of side effects may vary with the combination of anti-cancer medicines received):

Rare (may affect up to 1 in 1000 people)

- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Nivolumab

Summary of product characteristics

4.8 Undesirable effects

Table 6: Adverse reactions with nivolumab monotherapy

	Nivolumab monotherapy
Gastrointestinal disorders	
Rare	coeliac disease

Table 7: Adverse reactions with nivolumab in combination with other therapeutic agents

	Combination with ipilimumab (with or without chemotherapy)	**Combination with chemotherapy**	**Combination with cabozantinib**
Gastrointestinal disorders			
Rare	coeliac disease		
Not known		coeliac disease	coeliac disease

Package leaflet

4. Possible side effects

The following side effects have been reported **with OPDIVO alone**:

Rare (may affect up to 1 in 1000 people)

- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

The following side effects have been reported **with OPDIVO in combination with other anticancer medicines** (the frequency and severity of side effects may vary with the combination of anticancer medicines received):

Rare (may affect up to 1 in 1000 people)

- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Nivolumab/relatlimab

Summary of product characteristics

4.8 Undesirable effects

Tabulated summary of adverse reactions

Adverse reactions reported in the dataset for patients treated with nivolumab in combination with relatlimab, with a median follow-up of 19.94 months, are presented in Table 2. The frequencies included above and in Table 2 are based on all-cause adverse event frequencies. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions in clinical studies

Gastrointestinal disorders	
Not known	coeliac disease

Package leaflet

4. Possible side effects

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):

- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Atezolizumab

Summary of product characteristics

4.8 Undesirable effects

Table 3: Summary of adverse reactions occurring in patients treated with atezolizumab

Atezolizumab monotherapy		**Atezolizumab in combination therapy**
Gastrointestinal disorders		
Rare	Coeliac disease	Coeliac disease

Package leaflet

4. Possible side effects

Tecentriq used alone

The following side effects have been reported in clinical trials with Tecentriq used alone:

Rare: may affect up to 1 in 1,000 people

- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Tecentriq used in combination with anticancer medicines

The following side effects have been reported in clinical trials when Tecentriq is given in combination with anticancer medicines:

Rare: may affect up to 1 in 1,000 people

- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Tislelizumab

Summary of product characteristics

4.8 Undesirable effects

Table 2 Adverse reactions with Tevimbra as monotherapy (N = 1 534)

Adverse reactions	Frequency category (All grades)
Gastrointestinal disorders	
Coeliac disease	Rare

Package leaflet

4. Possible side effects

The following side effects have been reported with Tevimbra alone:

Rare: may affect up to 1 in 1,000 people

- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Durvalumab

Summary of product characteristics

4.8 Undesirable effects

Table 3. Adverse drug reactions in patients treated with IMFINZI

	IMFINZI as monotherapy	IMFINZI in combination with chemotherapy
Gastrointestinal disorders		
Rare	Coeliac disease	Coeliac disease

Table 4. Adverse drug reactions in patients treated with IMFINZI in combination with tremelimumab

	IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy	**IMFINZI in combination with tremelimumab 300 mg**
Gastrointestinal disorders		
Rare	Coeliac disease	Coeliac disease

Package leaflet

4. Possible side effects

Talk to your doctor straight away if you get any of the following side effects, that have been reported in clinical studies with patients receiving IMFINZI alone:

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

- Coeliac disease (characterized by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

The following side effects have been reported in clinical studies in patients taking IMFINZI in combination with chemotherapy (the frequency and severity of side effects may vary depending on chemotherapeutic agents received):

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

- Coeliac disease (characterized by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

The following side effects have been reported in clinical studies in patients taking IMFINZI in combination with tremelimumab and platinum-based chemotherapy (the frequency and severity of side effects may vary depending on chemotherapeutic agents received):

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

- Coeliac disease (characterized by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

The following side effects have been reported in clinical studies in patients taking IMFINZI in combination with tremelimumab:

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

- Coeliac disease (characterized by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Tremelimumab

Summary of product characteristics

4.8 Undesirable effects

Table 3. Adverse reactions in patients treated with tremelimumab in combination with durvalumab

	Tremelimumab 75 mg in combination with durvalumab and platinum-based chemotherapy		**Tremelimumab 300 mg in combination with durvalumab**		
	Any Grade (%)	**Grade 3-4 (%)**	**Any Grade (%)**	**Grade 3-4 (%)**	
Gastrointestinal disorders					
Coeliac disease	Rare[p]	0.03	0.03	Rare[p]	0.03	0.03

[p] Reported in studies outside of the POSEIDON study and HCC pool. Frequency is based on a pooled data set of patients treated with tremelimumab in combination with durvalumab

Package leaflet

4. Possible side effects

The following side effects have been reported in clinical trials in patients taking IMJUDO in combination with durvalumab:

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

- Coeliac disease (characterized by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

The following side effects have been reported in clinical trials in patients taking IMJUDO in combination with durvalumab and platinum-based chemotherapy:

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

- Coeliac disease (characterized by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Dostarlimab

Summary of product characteristics

4.8 Undesirable effects

Description of selected adverse reactions

Immune checkpoint inhibitor class effects

There have been cases of the following adverse reactions reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with dostarlimab: coeliac disease.

Package leaflet

4. Possible side effects

The following side effects have been reported with JEMPERLI alone.

Not known:

Frequency cannot be estimated from the available data:

- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

The following side effects have been reported with JEMPERLI when given in combination with carboplatin and paclitaxel.

Not known:

Frequency cannot be estimated from the available data:

- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Cemiplimab

Summary of product characteristics

4.8 Undesirable effects

Description of selected adverse reactions

Immune checkpoint inhibitor class effects

There have been cases of the following adverse reactions reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with cemiplimab: coeliac disease.

Package leaflet

4. Possible side effects

The following side effects have been reported in clinical trials of patients treated with cemiplimab alone:

Other side effects that have been reported (frequency not known):

- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

The following side effects have been reported in clinical trials of patients treated with cemiplimab in combination with chemotherapy:

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):

- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Avelumab

Summary of product characteristics

4.8 Undesirable effects

Description of selected adverse reactions

Immune checkpoint inhibitor class effects

There have been cases of the following adverse reactions reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with avelumab: coeliac disease.

Package leaflet

4. Possible side effects

The following side effects have been reported in clinical trials with avelumab alone:

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):

- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

The following side effects have been reported in clinical trials with avelumab in combination with axitinib:

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):

- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

3. Atezolizumab; avelumab; cemiplimab; dostarlimab; durvalumab; ipilimumab; nivolumab; nivolumab, relatlimab; pembrolizumab; tislelizumab; tremelimumab – Pancreatic failure (EPITT no 19955)

Nivolumab

Summary of product characteristics

4.8 Undesirable effects

Table 6: Adverse reactions with nivolumab monotherapy

	Nivolumab monotherapy
Gastrointestinal disorders	
Rare	Pancreatic exocrine insufficiency

Table 7: Adverse reactions with nivolumab in combination with other therapeutic agents

	Combination with ipilimumab (with or without chemotherapy)	**Combination with chemotherapy**	**Combination with cabozantinib**
Gastrointestinal disorders			
Rare	Pancreatic exocrine insufficiency		
Not known		Pancreatic exocrine insufficiency	Pancreatic exocrine insufficiency

Package leaflet

4. Possible side effects

The following side effects have been reported **with OPDIVO alone:**

Rare (may affect up to 1 in 1000 people)

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

The following side effects have been reported **with OPDIVO in combination with other anti-cancer medicines** (the frequency and severity of side effects may vary with the combination of anticancer medicines received):

Rare (may affect up to 1 in 1000 people)

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

Ipilimumab

Summary of product characteristics

4.8 Undesirable effects

Table 4: Adverse reactions in patients with advanced melanoma treated with ipilimumab 3 mg/kg

Gastrointestinal disorders	
Rare	Pancreatic exocrine insufficiency

Table 5: Adverse reactions with ipilimumab in combination with other therapeutic agents

	Combination with nivolumab (with or without chemotherapy)
Gastrointestinal disorders	
Rare	Pancreatic exocrine insufficiency

Package leaflet

4. Possible side effects

The following side effects have been reported in patients receiving 3 mg/kg ipilimumab alone:

Rare (may affect up to 1 in 1000 people)

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

The following side effects have been reported with ipilimumab in combination with other anti-cancer medicines (the frequency and severity of side effects may vary with the combination of anti-cancer medicines received):

Rare (may affect up to 1 in 1000 people)

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

Nivolumab/relatlimab

Summary of product characteristics

4.8 Undesirable effects

Table 2: Adverse reactions in clinical studies

Gastrointestinal disorders	
Rare	Pancreatic exocrine insufficiency

Package leaflet

4. Possible side effects

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

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

Pembrolizumab

Summary of product characteristics

4.8 Undesirable effects

Table 2: Adverse reactions in patients treated with pembrolizumab

	Monotherapy	**In combination with chemotherapy**	**In combination with axitinib or lenvatinib**
Gastrointestinal disorders			
Rare	pancreatic exocrine insufficiency	pancreatic exocrine insufficiency	
Not known			pancreatic exocrine insufficiency

Package leaflet

4. Possible side effects

The following side effects have been reported with pembrolizumab alone:

Rare (may affect up to 1 in 1000 people)

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency); a hole in the small intestines

The following side effects have been reported in clinical studies with pembrolizumab in combination with chemotherapy:

Rare (may affect up to 1 in 1000 people)

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency); a hole in the small intestines

The following side effects have been reported in clinical studies with pembrolizumab in combination with axitinib or lenvatinib:

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

Atezolizumab

Summary of product characteristics

4.8 Undesirable effects

Description of selected adverse reactions

Immune checkpoint inhibitor class effects

There have been cases of the following adverse reaction(s) reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with atezolizumab: pancreatic exocrine insufficiency

Package leaflet

4. Possible side effects

Tecentriq used alone

Other side effects that have been reported (not known: cannot be estimated from the available data):

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

Tecentriq used in combination with anticancer medicines

Other side effects that have been reported (not known: cannot be estimated from the available data)

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

Avelumab

Summary of product characteristics

4.8 Undesirable effects

Description of selected adverse reactions

Immune checkpoint inhibitor class effects

There have been cases of the following adverse reaction(s) reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with avelumab: pancreatic exocrine insufficiency

Package leaflet

4. Possible side effects

The following side effects have been reported in clinical trials with avelumab alone:

Other side effects that have been reported (frequency not known):

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

The following side effects have been reported in clinical trials with avelumab in combination with axitinib:

Other side effects that have been reported (frequency not known):

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

Cemiplimab

Summary of product characteristics

4.8 Undesirable effects

Description of selected adverse reactions

Immune checkpoint inhibitor class effects

There have been cases of the following adverse reaction(s) reported during treatment with other immune checkpoint inhibitors, which might also occur during treatment with cemiplimab: pancreatic exocrine insufficiency

Package leaflet

4. Possible side effects

The following side effects have been reported in clinical trials of patients treated with cemiplimab alone:

Other side effects that have been reported (frequency not known):

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

The following side effects have been reported in clinical trials of patients treated with cemiplimab in combination with chemotherapy:

Other side effects that have been reported (frequency not known):

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

Dostarlimab

Summary of product characteristics

4.8 Undesirable effects

Description of selected adverse reactions

Immune checkpoint inhibitor class effects

There have been cases of the following adverse reactions reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with dostarlimab: pancreatic exocrine insufficiency

Package leaflet

4. Possible side effects

The following side effects have been reported with JEMPERLI alone.

Other side effects that have been reported (frequency not known):

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

The following side effects have been reported with JEMPERLI when given in combination with carboplatin and paclitaxel.

Other side effects that have been reported (frequency not known):

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

Tislelizumab

Summary of product characteristics

4.8 Undesirable effects

Description of selected adverse reactions

Immune checkpoint inhibitor class effects

There have been cases of the following adverse reactions reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with tislelizumab: pancreatic exocrine insufficiency

Package leaflet

4. Possible side effects

The following side effects have been reported with Tevimbra alone:

Other side effects that have been reported (frequency not known):

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

Durvalumab

Summary of product characteristics

4.8 Undesirable effects

Description of selected adverse reactions

Immune checkpoint inhibitor class effects

There have been cases of the following adverse reactions reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with durvalumab: pancreatic exocrine insufficiency

Package leaflet

4. Possible side effects

Talk to your doctor straight away if you get any of the following side effects, that have been reported in clinical studies with patients receiving IMFINZI alone:

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)
Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

The following side effects have been reported in clinical studies in patients taking IMFINZI in combination with chemotherapy (the frequency and severity of side effects may vary depending on chemotherapeutic agents received):

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)
Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

The following side effects have been reported in clinical studies in patients taking IMFINZI in combination with tremelimumab and platinum-based chemotherapy (the frequency and severity of side effects may vary depending on chemotherapeutic agents received):

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)
Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

The following side effects have been reported in clinical studies in patients taking IMFINZI in combination with tremelimumab:

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)
Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

Tremelimumab

Summary of product characteristics

4.8 Undesirable effects

Description of selected adverse reactions

Immune checkpoint inhibitor class effects

There have been cases of the following adverse reactions reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with tremelimumab: pancreatic exocrine insufficiency

Package leaflet

4. Possible side effects

The following side effects have been reported in clinical trials in patients taking IMJUDO in combination with durvalumab:

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

The following side effects have been reported in clinical trials in patients taking IMJUDO in combination with durvalumab and platinum-based chemotherapy:

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)

Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

4. Chlorhexidine for cutaneous use, indicated for skin disinfection, and relevant fixed-dose combinations – Persistent corneal injury and significant visual impairment (EPITT no 19970)

*Text to be adapted by marketing authorisation holders to individual products**

Summary of product characteristics

4.4 Special warnings and precautions for use

~~Keep out of the eyes.~~

~~Chlorhexidine~~ <Product name> must not come into contact with the eye. Serious cases of persistent corneal injury, potentially requiring corneal transplant, were reported following accidental ocular exposure to chlorhexidine containing medicinal products despite taking eye protective measures due to migration of solution beyond the intended surgical preparation area. Extreme care must be taken during application to ensure that <Product name> does not migrate beyond its intended application site into the eyes. Particular care should be taken in anaesthetised patients, who are unable to immediately report ocular exposure. If ~~chlorhexidine solutions~~ <Product name> comes into contact with the eyes, wash out promptly and thoroughly with water. An ophthalmologist's advice should be sought.

4.8 Undesirable effects

Eye Disorder:

Frequency not known: Corneal erosion, epithelium defect/corneal injury, significant permanent visual impairment*.

Footnote: Cases of severe corneal erosion and permanent significant visual impairment due to inadvertent ocular exposure have been reported post-marketing, leading to some patients requiring corneal transplant (see section 4.4).

Package leaflet

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

Talk to your doctor, pharmacist or nurse before using <Product name>.

- Avoid contact with the ~~eyes,~~ brain, meninges (the membranes surrounding the brain and spinal cord) and middle ear.

- <Product name> must not come into contact with the eye due to the risk of visual damage. If it comes into contact with the eyes, wash out immediately and thoroughly with water. In case of any irritation, redness or pain in the eye, or visual disturbance, ask for medical advice promptly.

Serious cases of persistent corneal injury (injury to the surface of the eye) potentially requiring corneal transplant have been reported when similar products have accidentally come in contact with the eye during surgical procedures~~,~~ in patients under general anaesthesia (deep painless sleep).

4. Possible side effects

Other possible side effects, for which it is not known how often they occur, are:

- allergic skin disorders such as dermatitis (inflammation of the skin), pruritus (itch), erythema (redness of the skin), eczema, rash, urticaria (hives), skin irritation and blisters.

- corneal injury (injury to the surface of the eye), and permanent eye damage including permanent visual impairment (following accidental ocular exposure during head, face and neck surgical procedures) in patients under general anaesthesia (deep painless sleep).

** Due to differences in the national summaries of product characteristics and package leaflets, it is acknowledged that 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.*

5. Ethambutol – Drug reaction with eosinophilia and systemic symptoms (DRESS) (EPITT no 20018)

*Text to be adapted by marketing authorisation holders to individual products**

For products that have SJS and TEN included in their current summary of product characteristics (regardless of the section it is in):

Summary of product characteristics

4.4 Special warnings and precautions for use

Skin and subcutaneous tissue disorders

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported post-marketing in association with ethambutol treatment.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions.

If signs and symptoms suggestive of these reactions appear, ethambutol should be withdrawn immediately and an alternative treatment considered (as appropriate).

If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of ethambutol, treatment with ethambutol must not be restarted in this patient at any time.

For products with indication in children, the following paragraph should be added to this section 4.4:

In children, the presentation of a rash can be mistaken for the underlying infection or an alternative infectious process, and physicians should consider the possibility of a reaction to ethambutol in children that develop symptoms of rash and fever during therapy with ethambutol.

4.8 Undesirable effects

Skin and subcutaneous tissue disorders: Frequency: not known

drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4)

Package leaflet

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

DO NOT TAKE <PRODUCT NAME> - OR - TELL YOUR DOCTOR BEFORE TAKING <PRODUCT NAME>:

If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking ethambutol.

Warnings and precautions - Take special care with <product name>:

Serious skin reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with <product name> treatment. Stop taking <product name> and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

4. Possible side effects

Skin and subcutaneous skin disorders

Stop using <product name> and tell your doctor immediately if you notice any of the following symptoms:

- ~~Rash and strong local itching (pruritus), acute condition of the skin and mucous membranes associated is accompanied by serious symptoms and high fever, blisters on the oral mucosa, lips, eyes and genital organs (Stevens Johnson syndrome and toxic epidermal necrolysis)~~
- reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis).
- Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).

For products without SJS and TEN in their current SmPC:

Summary of product characteristics

4.4 Special warnings and precautions for use

Skin and subcutaneous tissue disorders

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported post-marketing in association with ethambutol treatment.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions.

If signs and symptoms suggestive of these reactions appear, ethambutol should be withdrawn immediately and an alternative treatment considered (as appropriate).

If the patient has developed a serious reaction such as DRESS with the use of ethambutol, treatment with ethambutol must not be restarted in this patient at any time.

For products with indication in children, the following paragraph should be added to this section 4.4:

In children, the presentation of a rash can be mistaken for the underlying infection or an alternative infectious process, and physicians should consider the possibility of a reaction to ethambutol in children that develop symptoms of rash and fever during therapy with ethambutol.

4.8 Undesirable effects

Skin and subcutaneous tissue disorders: Frequency: not known

drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4)

Package leaflet

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

DO NOT TAKE <PRODUCT NAME> - OR - TELL YOUR DOCTOR BEFORE TAKING <PRODUCT NAME>:

If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking ethambutol.

Warnings and precautions - Take special care with <product name>:

Serious skin reactions including drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with <product name> treatment. Stop taking <product name> and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

4. Possible side effects

Skin and subcutaneous skin disorders

Stop taking <product name> and tell your doctor immediately if you notice any of the following symptoms:

- Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).

** Due to differences in the national summaries of product characteristics and package leaflets, it is acknowledged that 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.*