



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 8-11 April 2024 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 8-11 April 2024 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT]² 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 (22-25 April 2024) 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.

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

² 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 information³

1.1. Adagrasib – Serious cutaneous adverse reactions (SCARs)

Authorisation procedure	Centralised
EPITT No	20051
PRAC Rapporteur	Kimmo Jaakkola (FI)
Date of adoption	11 April 2024

Recommendation [see also section 3]

Having considered the available evidence from case reports in EudraVigilance and literature, the PRAC has agreed that the Marketing Authorisation Holder (MAH) of Krazati, Mirati Therapeutics B.V. 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

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.

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).

³ 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. Atezolizumab; avelumab; cemiplimab; dostarlimab; durvalumab; ipilimumab; nivolumab; nivolumab, relatlimab; pembrolizumab; tislelizumab; tremelimumab – Coeliac disease

Authorisation procedure	Centralised
EPITT No	19958
PRAC Rapporteur	Bianca Mulder (NL)
Date of adoption	11 April 2024

Recommendation

Having considered the available evidence in EudraVigilance, clinical studies and the literature, including the cumulative reviews submitted by the Marketing Authorisation Holders (MAH), and a biologically plausible mechanism, the PRAC has agreed that the MAHs of the following (monotherapy and/or combination therapy as applicable): nivolumab (Opdivo, Opdualag) (Bristol-Myers Squibb Pharma EEIG), pembrolizumab (Keytruda) (Merck Sharp & Dohme B.V.), durvalumab (Imfinzi) (AstraZeneca AB), avelumab (Bavencio) (Merck Europe B.V.), atezolizumab (Tecentriq) (Roche Registration GmbH), cemiplimab (Libtayo) (Regeneron Ireland Designated Activity Company (DAC)), dostarlimab (Jemperli) (GlaxoSmithKline (Ireland) Limited), tislelizumab (Tevimbra) (Beigene Ireland Limited), ipilimumab (Yervoy) (Bristol-Myers Squibb Pharma EEIG) and tremelimumab (Imjudo) (AstraZeneca AB) 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):

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, <u>coeliac disease</u>	small intestinal perforation, <u>coeliac disease</u>	small intestinal perforation
<u>Not known</u>			<u>coeliac disease</u>

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)

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	<u>coeliac disease</u>

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

	Combination with nivolumab (with or without chemotherapy)
Gastrointestinal disorders	
Rare	<u>coeliac disease</u>

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	<u>coeliac disease</u>

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	<u>coeliac disease</u>		
<u>Not known</u>		<u>coeliac disease</u>	<u>coeliac disease</u>

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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	
<u>Not known</u>	<u>coeliac disease</u>

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		
<u>Rare</u>	<u>Coeliac disease</u>	<u>Coeliac disease</u>

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	
<u>Coeliac disease</u>	<u>Rare</u>

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		
<u>Rare</u>	<u>Coeliac disease</u>	<u>Coeliac disease</u>

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		
<u>Rare</u>	<u>Coeliac disease</u>	<u>Coeliac disease</u>

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						
<u>Coeliac disease</u>	Rare ^P	<u>0.03</u>	<u>0.03</u>	Rare ^P	<u>0.03</u>	<u>0.03</u>

^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)

1.3. Atezolizumab; avelumab; cemiplimab; dostarlimab; durvalumab; ipilimumab; nivolumab; nivolumab, relatlimab; pembrolizumab; tislelizumab; tremelimumab – Pancreatic failure

Authorisation procedure	Centralised
EPITT No	19955
PRAC Rapporteur	Martin Huber (DE)
Date of adoption	11 April 2024

Recommendation

Having considered the available evidence from case reports in EudraVigilance, clinical studies and the literature, including the cumulative reviews submitted by the Marketing Authorisation Holder/s (MAH/s), the PRAC has agreed that the MAHs of the nivolumab-containing products Opdivo and Opdualag (Bristol-Myers Squibb Pharma EEIG), pembrolizumab (Keytruda) (Merck Sharp & Dohme B.V.), durvalumab (Imfinzi) (AstraZeneca AB), avelumab (Bavencio) (Merck Europe B.V.), atezolizumab (Tecentriq) (Roche Registration GmbH), cemiplimab (Libtayo) (Regeneron Ireland Designated Activity Company (DAC)), dostarlimab (Jemperli) (GlaxoSmithKline (Ireland) Limited), tislelizumab (Tevimbra) (Novartis Europharm Limited), ipilimumab (Yervoy) (Bristol-Myers Squibb Pharma EEIG) and tremelimumab (Imjudo) (AstraZeneca AB) 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):

Nivolumab

Summary of product characteristics

4.8 Undesirable effects

Table 6: Adverse reactions with nivolumab monotherapy

	Nivolumab monotherapy
Gastrointestinal disorders	
Rare	<u>Pancreatic exocrine insufficiency</u>

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	<u>Pancreatic exocrine insufficiency</u>		
<u>Not known</u>		<u>Pancreatic exocrine insufficiency</u>	<u>Pancreatic exocrine insufficiency</u>

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	
<u>Rare</u>	<u>Pancreatic exocrine insufficiency</u>

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

	Combination with nivolumab (with or without chemotherapy)
Gastrointestinal disorders	
<u>Rare</u>	<u>Pancreatic exocrine insufficiency</u>

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	
<u>Rare</u>	<u>Pancreatic exocrine insufficiency</u>

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			
<u>Rare</u>	<u>pancreatic exocrine insufficiency</u>	<u>pancreatic exocrine insufficiency</u>	
<u>Not known</u>			<u>pancreatic exocrine insufficiency</u>

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)

1.4. Chlorhexidine for cutaneous use, indicated for skin disinfection, and relevant fixed-dose combinations⁴ – Persistent corneal injury and significant visual impairment

Authorisation procedure	Non-centralised
EPITT No	19970
PRAC Rapporteur	Lina Šeibokienė (LT)
Date of adoption	11 April 2024

Recommendation

Having considered the available evidence in EudraVigilance, literature and cumulative reviews submitted by Marketing Authorisation Holders (MAHs), PRAC has agreed that all MAHs of chlorhexidine monocomponent and fixed-combination containing products indicated for skin disinfection and intended for cutaneous use should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as applicable (taking into account the already

⁴ Chlorhexidine, chlorocresol, hexamidine; chlorhexidine gluconate, chlorocresol, hexamidine; chlorocresol, hexamidine, chlorhexidine digluconate; benzalkonium chloride, chlorhexidine gluconate; chlorhexidine gluconate, benzoxonium chloride, retinol; benzalkonium chloride, chlorhexidine gluconate, benzyl alcohol; chlorhexidine gluconate; chlorhexidine gluconate, cetrimonium; chlorhexidine gluconate, chlorocresol, hexamidine; chlorhexidine gluconate, dexpanthenol; chlorhexidine gluconate, hydrocortisone; chlorhexidine gluconate, hydrogen peroxide, isopropyl alcohol; chlorhexidine gluconate, isopropyl alcohol; chlorhexidine gluconate, ethanol; chlorhexidine gluconate, phenol; benzalkonium chloride, chlorhexidine gluconate; benzalkonium chloride, chlorhexidine digluconate; chlorhexidine digluconate, ethanol; chlorhexidine digluconate, isopropyl alcohol; chlorhexidine dihydrochloride; benzalkonium chloride, chlorhexidine dihydrochloride, isopropyl myristate, liquid paraffin; chlorhexidine dihydrochloride, dexpanthenol; chlorhexidine dihydrochloride, nystatin; chlorhexidine dihydrochloride, nystatin, dexamethasone; chlorhexidine dihydrochloride, nystatin, hydrocortisone; chlorhexidine dihydrochloride, zinc oxide, pramocaine hydrochloride; triamcinolone acetonide; chlorhexidine dihydrochloride, dexpanthenol, alphatocopherol acetate, vitamin A; chlorhexidine gluconate; cetrimide, chlorhexidine digluconate; chlorhexidine acetate; cetrimide, chlorhexidine acetate; retinol palmitate, chlorhexidine acetate; retinol palmitate, benzocaine, retinol, chlorhexidine acetate; bacitracin zinc, chlorhexidine acetate; nystatin, hydrocortisone, chlorhexidine acetate.

existing wording in some nationally authorised products), and described below (new text underlined, text to be adapted by MAHs 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 SmPCs 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.

1.5. Ethambutol – Drug reaction with eosinophilia and systemic symptoms (DRESS)

Authorisation procedure	Non-centralised
EPITT No	20018
PRAC Rapporteur	Sonja Hrabcik (AT)
Date of adoption	11 April 2024

Recommendation

Having considered the available evidence in EudraVigilance, including the cumulative review submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that all MAHs of ethambutol containing products, including single ingredients and combinations 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). Taking into account the already existing wording in some nationally authorised products, the text needs to be adapted by MAHs to individual products.

For products that have SJS and TEN included in their current SmPC (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).

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Anakinra	Amyloidosis (20073)	Karin Erneholm (DK)	Supplementary information requested (submission by 3 July 2024)	Swedish Orphan Biovitrum AB
Apalutamide	Lichenoid keratosis (20060)	Tiphaine Vaillant (FR)	Assess in the next PSUR (submission by 23 April 2024)	Janssen-Cilag International N.V.
Doxycycline	Suicidality (19997)	Liana Martirosyan (NL)	Supplementary information requested (submission by 3 July 2024)	Pfizer Limited
Eptinezumab; erenumab; fremanezumab; galcanezumab	Erectile dysfunction (20074)	Kirsti Villikka (FI)	Supplementary information requested (submission by 3 July 2024)	H. Lundbeck A/S, Novartis Europharm Limited, Teva GmbH, Eli Lilly Nederland B.V.
Pirfenidone	Lichenoid drug eruption (20069)	Rhea Fitzgerald (IE)	Assess in the next PSUR (submission by 27 May 2024)	Roche Registration GmbH
Posaconazole	Photosensitivity reaction (20076)	Nathalie Gault (FR)	Assess in the ongoing PSUR (submission of data by 17 April 2024 within the MAH comments to the PSUR preliminary assessment report)	MAHs of posaconazole with the obligation to submit PSURs

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adagrasib	Serious cutaneous adverse reactions (SCARs) (20051)	Kimmo Jaakkola (FI)	<ul style="list-style-type: none"> · See section 1.1 · Discuss new cases of SCARs in the next PSUR (submission by 20 August 2024) 	Mirati Therapeutics B.V.
Axicabtagene ciloleucel; idecabtagene vicleucel; lisocabtagene maraleucel; ciltabtagene autoleucel; tisagenlecleucel; brexucabtagene autoleucel	Secondary malignancy of T-cell origin (20040)	Ulla Wändel Liminga (SE)	Respond to list of questions (submission by 8 May 2024)	Bristol-Myers Squibb Pharma EEIG, Janssen-Cilag International NV, Novartis Europharm Limited, Kite Pharma EU B.V.
Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide; exenatide; liraglutide; insulin degludec, liraglutide; lixisenatide; insulin glargine, lixisenatide; semaglutide	Suicidal ideation and self-injurious ideation (19946)	Bianca Mulder (NL)	Routine pharmacovigilance	Novo Nordisk A/S, AstraZeneca AB, Eli Lilly Nederland B.V., Sanofi Winthrop Industrie
Teriparatide	Alopecias (19972)	Tiphaine Vaillant (FR)	Routine pharmacovigilance	MAHs of teriparatide-containing medicinal products