



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

6 April 2020<sup>1</sup>  
EMA/PRAC/111214/2020 Corr<sup>2,3,4</sup>  
Pharmacovigilance Risk Assessment Committee (PRAC)

## PRAC recommendations on signals

### Adopted at the 9-12 March 2020 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 9-12 March 2020 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT]<sup>5</sup> reference numbers).

PRAC recommendations to provide supplementary information are directly actionable by the concerned marketing authorisation holders (MAHs). PRAC recommendations for regulatory action (e.g. amendment of the product information) are submitted to the Committee for Medicinal Products for Human Use (CHMP) for endorsement when the signal concerns Centrally Authorised Products (CAPs), and to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for information in the case of Nationally Authorised Products (NAPs). Thereafter, MAHs are expected to take action according to the PRAC recommendations.

When appropriate, the PRAC may also recommend the conduct of additional analyses by the Agency or Member States.

MAHs are reminded that in line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, they shall ensure that their product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations published on the European Medicines Agency (EMA) website (currently acting as the EU medicines webportal).

For CAPs, at the time of publication, PRAC recommendations for update of product information have been agreed by the CHMP at their plenary meeting (23-26 March 2020) 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.

---

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

<sup>2</sup> Change in MAHs concerned for the signal on thiazide and thiazide-like diuretics (see page 7).

<sup>3</sup> A footnote was deleted on 8 April 2020 for the signal on thiazide and thiazide-like diuretics (see page 7).

<sup>4</sup> A minor edit was implemented in the product information of the signal on thiazide and thiazide-like diuretics on 5 June 2020 (see page 8).

<sup>5</sup> The relevant EPITT reference number should be used in any communication related to a signal.



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.

The timeline recommended by PRAC for submission of variations following signal assessment is applicable to both innovator and generic medicinal products, unless otherwise specified.

For procedural aspects related to the handling of PRAC recommendations on signals (e.g. submission requirements, contact points, etc.) please refer to the [Questions and Answers on signal management](#).

# 1. Recommendations for update of the product information<sup>6</sup>

## 1.1. Immune check point inhibitors: atezolizumab; cemiplimab; durvalumab – Tuberculosis

<b>Authorisation procedure</b>	Centralised
<b>EPITT No</b>	19464
<b>PRAC rapporteur(s)</b>	Brigitte Keller-Stanislowski (DE)
<b>Date of adoption</b>	12 March 2020

### Recommendation [see also section 3]

Having considered the available evidence from the cumulative review provided by the Marketing Authorisation Holders (MAHs) of Keytruda (Merck Sharp & Dohme B.V.), Opdivo and Yervoy (Bristol-Myers Squibb Pharma EEIG ), Tecentriq (Roche Registration GmbH ), Bavencio (Merck Europe B.V.), Imfinzi (AstraZeneca AB) and Libtayo (Regeneron Ireland), the PRAC has agreed the following recommendation:

[...]

Given the poor prognosis of Mycobacterium tuberculosis reactivation, the PRAC discussed the need to highlight in section 4.4 of the SmPC that infectious and disease-related aetiologies should be ruled out in patients with signs and symptoms suggestive for immune-related pneumonitis. Therefore, the MAHs for Imfinzi, Libtayo and Tecentriq should submit a variation within 2 months, to amend the product information as described below (new text to be added underlined, text to be removed ~~strike-through~~):

### IMFINZI (durvalumab)

#### Summary of product characteristics

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

##### Immune-mediated pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMFINZI.

Radiation pneumonitis is frequently observed in patients receiving radiation therapy to the lung and the clinical presentation of pneumonitis and radiation pneumonitis is very similar. In the PACIFIC Study, in patients who had completed treatment with at least 2 cycles of concurrent chemoradiation within 1 to 42 days prior to initiation of the trial, pneumonitis or radiation pneumonitis occurred in 161 (33.9%) patients in the IMFINZI-treated group and 58 (24.8%) in the placebo group, including Grade 3 (3.4% vs 3.0%) and Grade 5 (1.1% vs 1.7%) (see section 4.8).

Patients should be monitored for signs and symptoms of pneumonitis or radiation pneumonitis.

~~Patients with s~~Suspected pneumonitis should be evaluated confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as recommended in section 4.2.

<sup>6</sup> Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the [EMA website](#).

## **LIBTAYO (cemiplimab)**

### **Summary of product characteristics**

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

##### Immune-related adverse reactions

Severe and fatal immune-related adverse reactions have been observed with cemiplimab (see section 4.8). These immune-related reactions may involve any organ system. Most immune-related reactions initially manifest during treatment with cemiplimab; however, immune-related adverse reactions can occur after discontinuation of cemiplimab.

Immune-related adverse reactions should be managed with cemiplimab treatment modifications, hormone replacement therapy (if clinically indicated), and corticosteroids. For suspected immune-related adverse reactions, patients should be evaluated to confirm an immune-related adverse reaction and to exclude other possible causes, including infection. Depending upon the severity of the adverse reaction, cemiplimab should be withheld or permanently discontinued (see section 4.2).

##### Immune-related pneumonitis

Immune-related pneumonitis, defined as requiring use of corticosteroids with no clear alternate aetiology, including fatal cases, has been observed in patients receiving cemiplimab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis and causes other than immune-related pneumonitis should be ruled out.

Patients with suspected pneumonitis should be evaluated with radiographic imaging as indicated based on clinical evaluation and managed with cemiplimab treatment modifications and corticosteroids. (see section 4.2).

## **TECENTRIQ (atezolizumab)**

### **Summary of product characteristics**

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

##### Immune-related pneumonitis

Cases of pneumonitis, including fatal cases, have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis and causes other than immune-related pneumonitis should be ruled out.

Treatment with atezolizumab should be withheld for Grade 2 pneumonitis, and 1 to 2 mg/kg/day prednisone or equivalent should be started. If symptoms improve to  $\leq$  Grade 1, corticosteroids should be tapered over  $\geq$  1 month. Treatment with atezolizumab may be resumed if the event improves to  $\leq$  Grade 1 within 12 weeks, and corticosteroids have been reduced to  $\leq$  10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 pneumonitis.

## 1.2. Nivolumab – Haemophagocytic lymphohistiocytosis<sup>7</sup>

<b>Authorisation procedure</b>	Centralised
<b>EPITT No</b>	19467
<b>PRAC rapporteur(s)</b>	Brigitte Keller-Stanislowski (DE)
<b>Date of adoption</b>	13 February 2020

### Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the MAH of Opdivo (Bristol-Myers Squibb Pharma EEIG) 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

Haemophagocytic lymphohistiocytosis (HLH) has been observed with nivolumab as monotherapy and nivolumab in combination with ipilimumab. Caution should be taken when nivolumab is administered as monotherapy or in combination with ipilimumab. If HLH is confirmed, administration of nivolumab or nivolumab in combination with ipilimumab should be discontinued and treatment for HLH initiated.

##### 4.8. Undesirable effects

Table 5: Adverse reactions with nivolumab monotherapy

Blood and lymphatic system disorders

Haemophagocytic lymphohistiocytosis (Frequency 'Not known')

Table 6: Adverse reactions with nivolumab in combination with ipilimumab

Blood and lymphatic system disorders

Haemophagocytic lymphohistiocytosis (Frequency 'Not known')

#### Package leaflet

##### 2. What you need to know before you use OPDIVO

Warnings and precautions

Haemophagocytic lymphohistiocytosis. A rare disease in which our immune system makes too many of otherwise normal infection fighting cells called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems.

##### 4. Possible side effects

The following side effects have been reported with nivolumab alone:

---

<sup>7</sup> This signal was discussed at the 10-13 February 2020 PRAC meeting.

A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)

The following side effects have been reported with nivolumab in combination with ipilimumab:

A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)

### **1.3. Paroxetine – Microscopic colitis**

<b>Authorisation procedure</b>	Non-centralised
<b>EPITT No</b>	19474
<b>PRAC rapporteur(s)</b>	Liana Gross-Martirosyan (NL)
<b>Date of adoption</b>	12 March 2020

## **Recommendation**

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the MAHs of paroxetine-containing medicinal products 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**

#### 4.8. Undesirable effects

Gastrointestinal disorders

Frequency “not known”: Colitis microscopic

### **Package leaflet**

#### 4. Possible side effects

Side effects of which the frequency is not known:

Inflammation of the colon (causing diarrhoea)

## 1.4. Thiazide, thiazide-like diuretics and combinations<sup>8</sup> – Choroidal effusion

<b>Authorisation procedure</b>	Centralised and non-centralised
<b>EPITT No</b>	19468
<b>PRAC rapporteur(s)</b>	Martin Huber (DE)
<b>Date of adoption</b>	12 March 2020

### Recommendation

Having considered the available evidence from Eudravigilance and the literature, the PRAC has agreed that the MAHs<sup>9</sup> of thiazide and thiazide-like diuretics containing products (mono-substances and fixed-dose 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).

The warning regarding acute myopia and secondary angle-closure glaucoma in section 4.4 of the SmPC of thiazide and thiazide-like diuretics should be amended by adding information on choroidal effusion. In case this warning is currently not included in the SmPC, the complete section should be added.

For the package leaflet, the term “fluid accumulation in the vascular layer of the eye (choroidal effusion)” should be added to the existing warning in sections 2 and 4. In case this full warning is currently not included in the package leaflet, the complete section should be added.

### Summary of product characteristics

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

Choroidal effusion, acute myopia and secondary angle-closure glaucoma:

Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy

#### 4.8. Undesirable effects

For hydrochlorothiazide-, chlortalidone- and indapamide-containing products:

Eye disorders: choroidal effusion (frequency not known)

For bendroflumethiazide, cicletanine, clopamide, cyclopenthiazide, hydroflumethiazide, metipamide, metolazone, xipamide-containing products (choroidal effusion has not yet been reported but is considered a class effect):

*c. Description of selected adverse reactions:*

Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.

<sup>8</sup> The footnote listing some of the active substances and combinations was deleted on 8 April 2020.

<sup>9</sup> All MAHs are concerned (the word ‘innovator’ was removed on 6 April 2020).

If cases are to be reported for these substances in the future, the appropriate procedure should be used to update the product information accordingly.

## **Package leaflet**

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

#### Warnings and precautions

Talk to your doctor, pharmacist, or nurse before taking [product name]

If you experience a decrease in vision or eye pain. These could be symptoms of fluid accumulation in the vascular layer of the eye (choroidal effusion) or an increase of pressure in your eye and can happen within hours to weeks<sup>10</sup> of taking [product name]. This can lead to permanent vision loss, if not treated. If you earlier have had a penicillin or sulfonamide allergy, you can be at higher risk of developing this.

### 4. Possible side effects

Decrease in vision or pain in your eyes due to high pressure (possible signs of fluid accumulation in the vascular layer of the eye (choroidal effusion) or acute angle-closure glaucoma)

---

<sup>10</sup> 'a week' was replaced by 'weeks' on 5 June 2020.



## 2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Apixaban	Erythema multiforme (19534)	Menno van der Elst (NL)	Assess in the next PSUR (submission by 26 July 2020)	Bristol-Myers Squibb / Pfizer EEIG
Dabigatran	Gastro-oesophagitis (19530)	Anette Kirstine Stark (DK)	Assess in the next PSUR (submission by 27 May 2020)	Boehringer Ingelheim International GmbH
Interferon alfa-2a; interferon alfa-2b; peginterferon alfa-2a; peginterferon alfa-2b	Neuromyelitis optica spectrum disorder (19532)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 4 June 2020)	Merck Sharp & Dohme B.V., Roche
Lamotrigine	Photosensitivity (19548)	Liana Gross-Martirosyan (NL)	Supplementary information requested (submission by 6 May 2020)	GlaxoSmithKline B.V.
Lopinavir, ritonavir	Adrenal dysfunction in infants (19527)	Adrien Inoubli (FR)	Supplementary information requested (submission by 6 May 2020)	AbbVie Deutschland GmbH & Co. KG

### 3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Amitriptyline; bupropion; citalopram; escitalopram; fluoxetine; mirtazapine; paroxetine; sertraline; trazodone; venlafaxine	Post-partum haemorrhage (19552)	Ulla Wändel Liminga (SE)	No action at this stage	Not applicable
Buprenorphine; buprenorphine, naloxone	Drug-drug interaction with serotonergic drugs leading to serotonin syndrome (19475)	Martin Huber (DE)	Provide comments to the proposed updates to the product information (submission by 8 April 2020)	L. Molteni & C. dei Fratelli Alitti Società di Esercizio S.p.A., Indivior Europe Limited
Hormone replacement therapy (HRT) <sup>11</sup>	New information on the known risk of breast cancer (19482)	Menno van der Elst (NL)	Provide comments to the proposed updates to the product information (submission by 8 April 2020)	MAHs of products containing oestrogens only and combined oestrogen-progestagen HRT products, HRT-products which are vaginally applied estrogens of which the systemic exposure remains within postmenopausal range, DUAVIVE and tibolone
Immune check point inhibitors: atezolizumab; avelumab; cemiplimab; durvalumab; ipilimumab; nivolumab; pembrolizumab	Tuberculosis (19464)	Brigitte Keller-Stanislawski (DE)	<ul style="list-style-type: none"> <li>· See section 1.1</li> <li>· Monitor Mycobacterium tuberculosis infection and reactivation as part of routine safety surveillance; monitor events of systemic bacillus Calmette-</li> </ul>	Roche Registration GmbH, Merck Europe B.V., Regeneron Ireland, AstraZeneca AB, Bristol-Myers Squibb Pharma EEIG, Merck

<sup>11</sup> Chlorotrianisene; conjugated estrogens; conjugated estrogens, bazedoxifene; dienestrol; diethylstilbestrol; estradiol; estradiol, norethisterone; estriol; estrone; ethinylestradiol; methallenestril; moxestrol; promestriene; tibolone

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
			Guérin (BCG) infection in patients with urothelial cancer, previously treated with BCG for immunotherapy as part of routine safety surveillance	Sharp & Dohme B.V.
Mycophenolic acid; mycophenolate mofetil	Posterior reversible encephalopathy syndrome (PRES) (19473)	Hans Christian Siersted (DK)	Routine pharmacovigilance	MAHs of mycophenolic acid and mycophenolate mofetil containing products