



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 31 August-3 September 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 31 August-3 September 2020 (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 (14-17 September 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.

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.



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 information³

1.1. Abiraterone – Anaphylactic reaction

Authorisation procedure	Centralised
EPITT No	19535
PRAC rapporteur(s)	Eva A. Segovia (ES)
Date of adoption	3 September 2020

Recommendation

Having considered the available evidence in EudraVigilance, in the literature and the data provided by the MAH, the PRAC has agreed that the MAH for Zytiga (Janssen-Cilag) 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

Immune system disorders

Frequency 'not known': anaphylactic reactions

Package leaflet

4. Possible side effects

Not known (frequency cannot be estimated from the available data):

Heart attack, changes in ECG - electrocardiogram (QT prolongation), and serious allergic reactions with difficulty swallowing or breathing, swollen face, lips, tongue or throat, or an itchy rash.

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. Fluoroquinolones for systemic and inhalation formulations⁴ – Heart valve regurgitation, cervical artery dissection, and aortic aneurysm and dissection

Authorisation procedure	Centralised and non-centralised
EPITT No	19522
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	3 September 2020

Recommendation [see also section 3]

PRAC has considered the evidences from the literature, EudraVigilance and the cumulative reviews provided by Sanofi and Bayer, regarding the risks of heart valve regurgitation/incompetence and of aortic aneurysm and dissection associated with the use of fluoroquinolones systemic and inhaled formulations.

PRAC agrees that there is sufficient data to support a causal association between fluoroquinolones treatment and the development of those safety concerns. Therefore, PRAC recommends that the Marketing Authorisation Holders (MAHs) for fluoroquinolones systemic and inhaled formulations should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as described hereafter (**new text underlined and in bold**, deleted text strike through):

Summary of product characteristics

4.4. Special warnings and precautions for use

Aortic aneurysm and dissection, **and heart valve regurgitation/incompetence**

Epidemiologic studies report an increased risk of aortic aneurysm and dissection, **particularly in elderly patients, and of aortic and mitral valve regurgitation** after intake of fluoroquinolones particularly in the older population. **Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.8).**

Therefore, fluoroquinolones should only be used after a careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease **or congenital heart valve disease**, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection **or heart valve disease**, or in presence of other risk factors or conditions predisposing

- for **both** aortic aneurysm and dissection **and heart valve regurgitation/incompetence** (e.g. **connective tissue disorders such as** Marfan syndrome **or** vascular Ehlers-Danlos syndrome, **Turner syndrome**, Takayasu arteritis, giant cell arteritis, Behçet's disease, hypertension, **rheumatoid arthritis** ~~known atherosclerosis~~) **or additionally**
- **for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally**
- **for heart valve regurgitation/incompetence (e.g. infective endocarditis).**

⁴ Ciprofloxacin; delafloxacin; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

4.8. Undesirable effects

SOC Cardiac disorders**

SOC Vascular disorders**

* Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see Section 4.4).

**** Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.4).**

Package leaflet

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

Warning and precautions

Talk to your doctor before taking [product name]:

[...]

- if you have been diagnosed with an enlargement or "bulge" of a large blood vessel (aortic aneurysm or large vessel peripheral aneurysm).

- if you have experienced a previous episode of aortic dissection (a tear in the aorta wall).

- if you have been diagnosed with leaking heart valves (heart valve regurgitation).

- if you have a family history of aortic aneurysm or aortic dissection or **congenital heart valve disease, or** other risk factors or predisposing conditions (e.g. connective tissue disorders such as Marfan syndrome, or vascular Ehlers-Danlos syndrome, **Turner syndrome, Sjögren's syndrome [an inflammatory autoimmune disease],** or vascular disorders such as Takayasu arteritis, giant cell arteritis, Behçet's disease, high blood pressure, or known atherosclerosis, **rheumatoid arthritis [a disease of the joints] or endocarditis [an infection of the heart]**).

[...]

While taking [product name]:

[...]

- If you feel sudden, severe pain in your abdomen, chest or back, **which can be symptoms of aortic aneurysm and dissection**, go immediately to an emergency room. **Your risk may be increased if you are being treated with systemic corticosteroids.**

- If you start experiencing a rapid onset of shortness of breath, especially when you lie down flat in your bed, or you notice swelling of your ankles, feet or abdomen, or a new onset of heart palpitations (sensation of rapid or irregular heartbeat), you should inform a doctor immediately.

4. Possible side effects

[...]

Very rare cases of long lasting (up to months or years) or permanent adverse drug reactions, such as tendon inflammations, tendon rupture, joint pain, pain in the limbs, difficulty in walking, abnormal sensations such as pins and needles, tingling, tickling, burning, numbness or pain (neuropathy), depression, fatigue, sleep disorders, memory impairment, as well as impairment of hearing, vision, and taste and smell have been associated with administration of quinolone and fluoroquinolone antibiotics, in some cases irrespective of pre-existing risk factors.

Cases of an enlargement and weakening of the aortic wall or a tear in the aortic wall (aneurysms and dissections), which may rupture and may be fatal, and of leaking heart valves have been reported in patients receiving fluoroquinolones. See also section 2.

1.3. Interferon alfa-2a; peginterferon alfa-2a – Neuromyelitis optica spectrum disorder

Authorisation procedure	Centralised and non-centralised
EPITT No	19532
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of adoption	3 September 2020

Recommendation [see also section 3]

Having considered the available evidence in EudraVigilance, literature and data obtained from the Marketing Authorisation Holders (MAHs) of IntronA, PegIntron, ViraferonPeg, Roferon-A, Pegasys, the PRAC has agreed that the MAH for Roferon-A and Pegasys (Roche) should submit a variation within 2 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.8. Undesirable effects

Eye disorders

Frequency “not known”: Optic neuritis

1.4. Pomalidomide – Progressive multifocal leukoencephalopathy (PML)

Authorisation procedure	Centralised
EPITT No	19546
PRAC rapporteur(s)	Eva A. Segovia (ES)
Date of adoption	3 September 2020

Recommendation [see also section 3]

Having considered the available evidence in EudraVigilance, in the literature and the data provided by the MAH, the PRAC has agreed that the MAH for Imnovid (Celgene Europe 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

Progressive multifocal leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy, including fatal cases, have been reported with pomalidomide. PML was reported several months to several years after starting the treatment with pomalidomide. Cases have generally been reported in patients taking concomitant dexamethasone or prior treatment with other immunosuppressive chemotherapy. Physicians should monitor patients at regular intervals and should consider PML in the differential diagnosis in patients with new or worsening neurological symptoms, cognitive or behavioural signs or symptoms. Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

The evaluation for PML should be based on neurological examination, magnetic resonance imaging of the brain, and cerebrospinal fluid analysis for JC virus (JCV) DNA by polymerase chain reaction (PCR) or a brain biopsy with testing for JCV. A negative JCV PCR does not exclude PML. Additional follow-up and evaluation may be warranted if no alternative diagnosis can be established.

If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed, pomalidomide must be permanently discontinued.

Package leaflet

2. What you need to know before you take Imnovid

[...]

Warnings and precautions

At any time during or after your treatment, tell your doctor or nurse immediately if you experience: blurred, loss of or double vision, difficulty speaking, weakness in an arm or a leg, a change in the way you walk or problems with your balance, persistent numbness, decreased sensation or loss of sensation, memory loss or confusion. These may all be symptoms of a serious and potentially fatal brain condition known as progressive multifocal leukoencephalopathy (PML). If you had these symptoms prior to treatment with Imnovid, tell your doctor about any change in these symptoms.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins): atorvastatin; fenofibrate, simvastatin; fluvastatin; lovastatin; pitavastatin; pravastatin; pravastatin sodium, fenofibrate; rosuvastatin; simvastatin	Bullous pemphigoid (19586)	Adrien Inoubli (FR)	Supplementary information requested (submission by 11 November 2020)	Pfizer Pharma PFE GmbH; Novartis Farma - Produtos Farmacêuticos S.A.; Vifor Pharma España S.L.; Kowa Pharmaceutical Europe GmbH; Exeltis Healthcare S.L; AstraZeneca AB; Merck Sharp & Dohme BV; Mylan IRE Healthcare Limited; Laboratoires SMB S.A.
Anastrozole	Depressed mood disorders (19592)	Zane Neikena (LV)	Supplementary information requested (submission by 11 November 2020)	AstraZeneca
Ceftriaxone	Hepatitis (19603)	Zane Neikena (LV)	Supplementary information requested (submission by 11 November 2020)	MAH for the innovator of ceftriaxone containing products
Chloroquine; hydroxychloroquine	Psychiatric disorders (19572)	Anette Kirstine Stark (DK)	Supplementary information requested (submission by 23 October 2020)	MAHs for the innovators of chloroquine and hydroxychloroquine containing products
Filgrastim	Immune reconstitution inflammatory syndrome (IRIS) (19587)	Kirsti Villikka (FI)	Supplementary information requested (submission by 11 November 2020)	Amgen, Pfizer, Hexal AG, Ratiopharm GmbH, Teva, Sandoz GmbH, Accord

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Pembrolizumab	Systemic scleroderma (19591)	Menno van der Elst (NL)	Supplementary information requested (submission by 11 November 2020)	Merck Sharp & Dohme B.V.
Sacubitril, valsartan	Psychosis and psychotic disorders (19600)	Anette Kirstine Stark (DK)	Assess in the next PSUR (submission by 9 October 2020)	Novartis Europharm Limited
Tofacitinib	Psychiatric disorders (19585)	Liana Gross-Martirosyan (NL)	Assess in the next PSUR (submission by 14 January 2021)	Pfizer Europe MA EEIG

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Fluoroquinolones for systemic and inhaled formulations: ciprofloxacin; delafloxacin; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin	Heart valve regurgitation, cervical artery dissection, and aortic aneurysm and dissection (19522)	Martin Huber (DE)	<ul style="list-style-type: none"> See section 1.2 Distribute a Direct Healthcare Professional Communication (DHPC) by 29 October 2020 Consider in PSURs the risks of heart valve regurgitation/ incompetence and of aortic aneurysm and dissection as important identified risks and provide information on the effectiveness of the new risk minimisation measures Closely monitor in PSURs the disorders of arteries other than the aorta 	MAHs of fluoroquinolones for systemic and inhaled formulations
Interferon alfa-2a; interferon alfa-2b; peginterferon alfa-2a; peginterferon alfa-2b	Neuromyelitis optica spectrum disorder (19532)	Ulla Wändel Liminga (SE)	<ul style="list-style-type: none"> See section 1.3 for interferon alfa-2a and peginterferon alfa-2a No action for interferon alfa-2b and peginterferon alfa-2b 	<ul style="list-style-type: none"> Roche MAHs of interferon alfa-2b and peginterferon alfa-2b containing

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
				products
Paclitaxel	Progressive multifocal leukoencephalopathy (PML) (19553)	Menno van der Elst (NL)	Monitor in PSUR	MAHs of paclitaxel-containing products
Pembrolizumab	Vasculitis (19578)	Menno van der Elst (NL)	Provide comments to the proposed updates to the product information and estimate the frequency of vasculitis (submission by 23 October 2020)	Merck Sharp & Dohme B.V.
Pomalidomide	Progressive multifocal leukoencephalopathy (PML) (19546)	Eva A. Segovia (ES)	<ul style="list-style-type: none"> • See section 1.4 • Monitor PML in future PSURs as an independent topic 	Celgene Europe B.V.
Vedolizumab	Evans' syndrome, autoimmune haemolytic anaemia, immune thrombocytopenic purpura (19547)	Adam Przybylowski (PL)	Monitor in PSUR	Takeda Pharma A/S