



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 August 2019¹
EMA/PRAC/347675/2019
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 8-11 July 2019 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 July 2019 (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 July 2019) 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 Intended 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. Parenteral nutrition products⁴ containing amino acids and/or lipids with or without admixture of vitamins and/or trace elements – Adverse outcomes in neonates treated with solutions not protected from light

Authorisation procedure	Non-centralised
EPITT No	19423
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of adoption	11 July 2019

Recommendation [see also section 3]

The PRAC has reviewed the data submitted by marketing authorisation holders for parenteral nutrition products containing amino acids and/or lipids regarding the risk of toxic degradations of ingredients which may lead to severe clinical outcomes in premature neonates, when the products have been exposed to light. The PRAC agreed on the need for updating the product information with recommendations on light protection when the solution is to be used in neonates and in children below 2 years of age until administration is completed. Furthermore, the PRAC agreed on the need for a direct healthcare professional communication (DHPC).

The MAHs of parenteral nutrition products containing amino acids and/or lipids with or without admixture of vitamins and/or trace elements and indicated in neonates and children below 2 years should submit a variation within 2 months to amend their products information as described below (new text underlined).

Summary of product characteristics

(* include neonates and if product is indicated in such population)

4.2. Posology and method of administration

Method of administration

When used in <neonates and *> children below 2 years, the solution (in bags and administration sets) should be protected from light exposure until administration is completed (see sections 4.4, 6.3 and 6.6).

4.4. Special warnings and precautions for use

[For products indicated in neonates (age up to 28 days)]

Light exposure of solutions for intravenous parenteral nutrition, especially after admixture with trace elements and/or vitamins, may have adverse effects on clinical outcome in neonates, due to generation of peroxides and other degradation products. When used in neonates and children below 2 years, <product name> should be protected from ambient light until administration is completed (see sections 4.2, 6.3 and 6.6).

³ Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the EMA website.

⁴ Indicated in neonates and children below 2 years

[For products NOT indicated in neonates BUT in children below 2 years]

Light exposure of solutions for intravenous parenteral nutrition, especially after admixture with trace elements and/or vitamins, may lead to generation of peroxides and other degradation products. When used in children below 2 years, <product name> should be protected from ambient light until administration is completed (see sections 4.2, 6.3 and 6.6).

6.3. Shelf life

When used in <neonates and * > children below 2 years, the solution (in bags and administration sets) should be protected from light exposure until administration is completed (see sections 4.2, 4.4 and 6.6).

6.6. Special precautions for disposal

When used in <neonates and * > children below 2 years, protect from light exposure, until administration is completed. Exposure of <product name> to ambient light, especially after admixture with trace elements and/ or vitamins, generates peroxides and other degradation products that can be reduced by protection from light exposure (see sections 4.2, 4.4 and 6.3).

Package leaflet

(* include neonates and if product is indicated in such population)

[For products used in neonates and children below 2 years]

2. Warnings and precautions

When used in <neonates and * > children below 2 years, the solution (in bags and administration sets) should be protected from light exposure until administration is completed. Exposure of <product name> to ambient light, especially after admixtures with trace elements and/or vitamins, generates peroxides and other degradation products that can be reduced by protection from light exposure.

3. Method of administration

When used in <neonates and * > children below 2 years, the solution (in bags and administration sets) should be protected from light exposure until administration is completed (see section 2).

5. How to store <product name>

When used in <neonates and * > children below 2 years, the solution (in bags and administration sets) should be protected from light exposure until administration is completed (see section 2).

Section at the end of the package leaflet:

The following information is intended for medical or healthcare professionals only.

Method of administration:

When used in <neonates and * > children below 2 years, the solution (in bags and administration sets) should be protected from light exposure until administration is completed.

Special warnings and precautions for use:

[For products indicated in neonates (age up to 28 days)]

Light exposure of solutions for intravenous parenteral nutrition, especially after admixture with trace elements and/or vitamins, may have adverse effects on clinical outcome in neonates, due to generation of peroxides and other degradation products. When used in neonates and children below 2 years, <product name> should be protected from ambient light until administration is completed.

[For products NOT indicated in neonates BUT in children below 2 years]

Light exposure of solutions for intravenous parenteral nutrition, especially after admixture with trace elements and/or vitamins, may lead to generation of peroxides and other degradation products. When used in children below 2 years, <product name> should be protected from ambient light until administration is completed.

Special precautions for disposal and other handling:

When used in <neonates and * > children below 2 years, protect from light exposure, until administration is completed. Exposure of <product name> to ambient light, especially after admixtures with trace elements and/or vitamins, generates peroxides and other degradation products that can be reduced by protection from light exposure.

Labelling text

15. INSTRUCTIONS ON USE

(* include neonates and if product is indicated in such population)

When used in <neonates and * > children below 2 years, the solution (in bags and administration sets) should be protected from light exposure until administration is completed.

1.2. Mesalazine – Nephrolithiasis

Authorisation procedure	Non-centralised
EPI TT No	19405
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	11 July 2019

Recommendation

Based on the review of the data on the risk of nephrolithiasis with mesalazine, the PRAC has agreed that the MAH(s) of mesalazine-containing medicinal product(s) should submit a variation within 2 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions

Cases of nephrolithiasis have been reported with the use of mesalazine including stones with a 100% mesalazine content. It is recommended to ensure adequate fluid intake during treatment.

4.8. Undesirable effects

Renal and urinary disorders

Frequency not known: nephrolithiasis*

* See section 4.4 for further information

Package leaflet

2. Warnings and precautions

Kidney stones may develop with use of mesalazine. Symptoms may include pain in sides of abdomen and blood in urine. Take care to drink sufficient amount of liquid during treatment with mesalazine.

4. Possible side effects

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

- kidney stones and associated kidney pain (see also section 2)

1.3. Ondansetron – Signal of birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications

Authorisation procedure	Non-centralised
EPI TT No	19353
PRAC rapporteur(s)	Gabriela Jazbec (SI)
Date of adoption	11 July 2019

Recommendation [see also section 3]

Having considered the available information, including the responses from study authors (Zambelli and Huybrechts) and from innovator MAH of ondansetron (Novartis) to the PRAC list of questions and also considering the methodological quality of the studies, the PRAC has agreed the following:

All MAHs of ondansetron-containing medicinal products should submit a variation within 2 months of the publication date of the PRAC recommendation, to amend the product information as described below (new text underlined/text to be removed with ~~strikethrough~~).

Summary of product characteristics

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should consider the use of contraception.

Pregnancy

~~The safety of ondansetron for use in human pregnancy has not been established.~~ Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy.

In one cohort study including 1.8 million pregnancies, first trimester ondansetron use was associated with an increased risk of oral clefts (3 additional cases per 10 000 women treated; adjusted relative risk, 1.24, (95% CI 1.03-1.48)).

The available epidemiological studies on cardiac malformations show conflicting results.

~~Evaluation of experimental~~ Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. ~~the development of the embryo, or foetus, the course of gestation and peri-~~

and post-natal development. However, as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.

Ondansetron should not be used during the first trimester of pregnancy.

Package Leaflet

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

Pregnancy and breast-feeding

~~It is not known if <product name> is safe during pregnancy. You should not use <product name> during the first trimester of pregnancy. This is because <product name> can slightly increase the risk of a baby being born with cleft lip and/or cleft palate (openings or splits in the upper lip and/or the roof of the mouth).~~ If you are already pregnant, think you are might be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking <product name>. If you are a woman of childbearing potential you may be advised to use effective contraception.

1.4. Vascular Endothelial Growth Factor (VEGF) inhibitors for systemic administration⁵ – Artery dissections and aneurysms

Authorisation procedure	Centralised and non-centralised
EPITT No	19330
PRAC rapporteur(s)	Annika Folin (SE)
Date of adoption	11 July 2019

Recommendation

Having considered the available evidence, following the assessment of the EudraVigilance data and consultation with the MAHs, the PRAC has agreed that the product information for the Vascular Endothelial Growth Factor (VEGF) inhibitors for systemic administration should be updated to reflect the risk of aneurysms and artery dissections.

The MAHs of products authorised containing the substances listed below, should submit a variation within two months to amend the product information as described here (new text underlined/text to be removed with ~~striketrough~~).

Axitinib

Summary of product characteristics

4.4. Special warnings and precautions for use

Haemorrhage

In clinical studies with axitinib, haemorrhagic events were reported (see section 4.8).

Axitinib has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding, and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose. ~~Cases of ruptured aneurysms (including~~

⁵ Aflibercept; axitinib; bevacizumab; cabozantinib; lenvatinib; nintedanib; pazopanib; ponatinib; ramucirumab; regorafenib; sorafenib; sunitinib; tivozanib; vandetanib

~~pre-existing aneurysms) have been reported, some with fatal outcome. Before initiating axitinib therapy in patients with pre-existing aneurysms, this risk should be carefully considered.~~

Aneurysms and artery dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating Inlyta, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

4.8. Undesirable effects

Tabulated list of adverse reactions

Vascular disorders

Frequency 'Not known': Aneurysms and artery dissections

Footnotes:

^hIncluding activated partial thromboplastin time prolonged, anal haemorrhage, ~~aneurysm rupture~~, arterial haemorrhage...

Package leaflet

2. What you need to know before you take Inlyta

Warnings and precautions

Talk to your doctor or nurse before taking Inlyta:

If you suffer from bleeding problems.

Inlyta may increase your chance of bleeding. Tell your doctor if you have any bleeding, coughing up of blood or bloody sputum while on treatment with this medicine. ~~Tell your doctor if you have an aneurysm (an abnormal balloon-like swelling in the wall of an artery) before taking this medicine. Inlyta may increase the risk of a rupture.~~

If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.

4. Possible side effects

Bleeding. Tell your doctor right away if you have any of these symptoms or a serious bleeding problem during treatment with Inlyta: black tarry stools, coughing up of blood or bloody sputum, or change in your mental status. ~~Also, tell your doctor if you have been diagnosed with an aneurysm before taking this medicine.~~

Other side effects with Inlyta may include:

Frequency: 'Not known'

An enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections).

Lenvatinib

Summary of product characteristics

4.4. Special warnings and precautions for use

Aneurysms and artery dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating <product name>, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

4.8. Undesirable effects

Tabulated list of adverse reactions

Vascular disorders

Frequency Uncommon: ~~Aortic Dissection~~

Frequency 'Not known': Aneurysms and artery dissections

Package leaflet

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

Warnings and precautions

Talk to your doctor or nurse before taking <product name>:

If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.

Section 4 - Possible side effects

Other side effects include:

Uncommon

~~severe pain in the back, chest or abdomen associated with tearing in the wall of the aorta and internal bleeding~~

Frequency: 'Not known'

An enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections).

Sunitinib

Summary of product characteristics

4.4. Special warnings and precautions for use

~~Aortic aneurysms and dissections~~

Aneurysms and artery dissections

~~Cases of aortic aneurysm and/or dissection (including fatal outcome) have been reported. The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections.~~ Before initiating <product name> therapy, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

4.8. Undesirable effects

Tabulated list of adverse reactions

Vascular disorders

Frequency 'Not known': ~~Aortic aneurysms and dissections*~~

Frequency 'Not known': Aneurysms and artery dissections*

Package leaflet

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

Warnings and precautions

Talk to your doctor or nurse before taking <product name>:

- ~~If you have been diagnosed with an enlargement or "bulge" of the large blood aortic vessel known as aortic aneurysm.~~
- ~~If you have experienced a previous episode of a tear in the aortic wall known as aortic dissection.~~
- If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.

4. Possible side effects

Other side effects include:

Frequency: 'Not known'

~~An enlargement or "bulge" of the aortic vessel or a tear in the aortic wall (aortic aneurysms and dissections).~~

An enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections).

Aflibercept (Zaltrap), bevacizumab, cabozantinib, nintedanib, pazopanib, ponatinib, ramucirumab, regorafenib, sorafenib, tivozanib, vandetanib

Summary of product characteristics

4.4. Special warnings and precautions for use

Aneurysms and artery dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating <product name>, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

4.8. Undesirable effects

Tabulated list of adverse reactions

Vascular disorders

Frequency 'Not known': Aneurysms and artery dissections

Package leaflet

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

Warnings and precautions

Talk to your doctor or nurse before taking <product name>:

If you have high blood pressure (only applicable for products containing nintedanib and vandetanib as for the rest of the products, this warning is already included)

If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.

4. Possible side effects

Other side effects include:

Frequency: 'Not known'

An enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections).

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Imiquimod	Pemphigus, new onset and relapse (19441)	Adam Przybylkowski (PL)	Supplementary information requested (submission by 28 August 2019)	Meda AB

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Parenteral nutrition products ⁶ containing amino acids and/or lipids with or without admixture of vitamins and/or trace elements	Adverse outcomes in neonates treated with solutions not protected from light (19423)	Ulla Wändel Liminga (SE)	<ul style="list-style-type: none">· See section 1.1· Distribute a direct healthcare professional communication (DHPC) with one MAH acting as contact point for the national competent authority in each member state on behalf of the other MAHs	MAHs of parenteral nutrition products containing amino acids and/or lipids with or without admixture of vitamins and/or trace elements

⁶ Indicated in neonates and children below 2 years

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Natalizumab	Psoriasis (19365)	Brigitte Keller-Stanislawski (DE)	Routine pharmacovigilance	Biogen Netherlands B.V.
Ondansetron; other 5-HT3 receptor antagonists: granisetron, palonosetron, palonosetron/netupitant, tropisetron	Signal of birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications (19353)	Gabriela Jazbec (SI)	<ul style="list-style-type: none"> · See section 1.3 · Agree on communication at national level with national competent authorities · Assess in the next PSUR (submission by 22 October 2019 for palonosetron, 19 December 2019 for netupitant / palonosetron, 28 December 2019 for granisetron [transdermal patch], 19 May 2021 for granisetron [other formulations except transdermal patch], according to the national PSUR cycle for tropisetron 	<ul style="list-style-type: none"> · MAHs of ondansetron containing products · Innovator MAH for ondansetron (Novartis) · MAHs of granisetron, palonosetron, palonosetron/netupitant and tropisetron containing products