5 August 2019[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 8-11 July 2019 PRAC

The product information wording in this document is extracted from the document entitled 'PRAC recommendations on signals' which contains the whole text of the PRAC recommendations for product information update, as well as some general guidance on the handling of signals. It can be found ***here*** (in English only).

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

1. Parenteral nutrition products[2] 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 (EPITT no 19423)

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)]

[1] Intended publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.
[2] Indicated in neonates and children below 2 years

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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).

[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.

2. Mesalazine – Nephrolithiasis (EPITT no 19405)

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)

3. Ondansetron – Signal of birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications (EPITT no 19353)

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.

4. Vascular Endothelial Growth Factor (VEGF) inhibitors for systemic administration[3] – Artery dissections and aneurysms (EPITT no 19330)

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 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:

[h]Including 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.~~

[3] Aflibercept; axitinib; bevacizumab; cabozantinib; lenvatinib; nintedanib; pazopanib; ponatinib; ramucirumab; regorafenib; sorafenib; sunitinib; tivozanib; vandetanib

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.

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).