20 July 2017
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 3-6 July 2017 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 3-6 July 2017 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][1] 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 (17-20 July 2017) 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] The relevant EPITT reference number should be used in any communication related to a signal.

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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[2]

1.1. Amoxicillin; amoxicillin, clavulanic acid – Drug reaction with eosinophilia and systemic symptoms (DRESS)

Authorisation procedure	Non-centralised
EPITT No	18802
PRAC rapporteur(s)	Jan Neuhauser (AT)
Date of adoption	6 July 2017

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the MAH(s) of amoxicillin-containing medicinal products should submit a variation within 2 months, to amend the product information as described below (new text underlined).

Amoxicillin

Summary of product characteristics

4.4. Special warnings and precautions for use

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy.

4.8. Undesirable effects

Skin and subcutaneous tissue disorders

Frequency 'very rare': Skin reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis, ~~and~~ acute generalized exanthematous pustulosis (AGEP) (see section 4.4) and drug reaction with eosinophilia and systemic symptoms (DRESS).

Package leaflet

4. Possible side effects

Very rare

- other severe skin reactions can include: changes in skin colour, bumps under the skin, blistering, pustules, peeling, redness, pain, itching, scaling. These may be associated with fever, headaches and body aches
- flu-like symptoms with a rash, fever, swollen glands, and abnormal blood test results (including increased white blood cells (eosinophilia) and liver enzymes) (Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)).

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

Amoxicillin + clavulanic acid

Summary of product characteristics

4.4. Special warnings and precautions for use

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy.

4.8. Undesirable effects

Skin and subcutaneous tissue disorders

Frequency 'Not known': Drug reaction with eosinophilia and systemic symptoms (DRESS)

Package leaflet

4. Possible side effects

Frequency not known

- Serious skin reactions:
  - a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (*Stevens-Johnson syndrome*), and a more severe form, causing extensive peeling of the skin (more than 30% of the body surface *toxic epidermal necrolysis*)
  - widespread red skin rash with small pus-containing blisters (*bullous exfoliative dermatitis*)
  - a red, scaly rash with bumps under the skin and blisters (*exanthemous pustulosis*)
  - flu-like symptoms with a rash, fever, swollen glands, and abnormal blood test results (including increased white blood cells (eosinophilia) and liver enzymes) (Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS))

1.2. Ciprofloxacin; meropenem – Incompatibility leading to possible precipitation when co-administered intravenously

Authorisation procedure	Non-centralised
EPITT No	18790
PRAC rapporteur(s)	Jan Neuhauser (AT)
Date of adoption	6 July 2017

Recommendation

Having considered the available evidence in EudraVigilance, literature and the data provided by originator MAHs of ciprofloxacin and meropenem (Bayer and Astra Zeneca) , the PRAC has agreed that a plausible cause of incompatibility and precipitate formation might be the pH difference between the two medications. The information for preventing precipitate formation, given that the label instructions are followed, is adequately reflected in Summary of Product Characteristics of both Ciproxin and Meronem. The MAHs of all other ciprofloxacin and meropenem containing medicinal products (solutions for infusion) should submit a variation within 3 months to amend their product

information, if appropriate, to contain the warning in section 6.2 of their Summaries of Product Characteristics, as described below for originators:

1) Ciproxin solution for infusion

Summary of product characteristics

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Unless compatibility with other solutions/drugs has been confirmed, the infusion solution must always be administered separately. The visual signs of incompatibility are e.g. precipitation, clouding, and discoloration.

Incompatibility appears with all infusion solutions/drugs that are physically or chemically unstable at the pH of the solutions (e.g. penicillins, heparin solutions), especially in combination with solutions adjusted to an alkaline pH (pH of ciprofloxacin solutions: 3.9 – 4.5).

2) Meronem IV

Summary of product characteristics

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

1.3. Darbepoetin alfa; epoetin alfa; epoetin beta; epoetin theta; epoetin zeta; methoxy polyethylene glycol-epoetin beta – Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Authorisation procedure	Centralised and non-centralised
EPITT No	18846
PRAC rapporteur(s)	Valerie Straßmann (DE)
Date of adoption	6 July 2017

Recommendation *[see also section 3]*

Having considered the evidence provided by the MAHs of epoetin-containing medicinal products, the PRAC recommended that the MAHs of darbepoetin alfa (Aranesp - Amgen Europe B.V.), epoetin alfa (Abseamed - Medice Arzneimittel Pütter GmbH & Co. KG, Binocrit - Sandoz GmbH, Epoetin Alfa Hexal - Hexal AG, Eprex – Janssen-Cilag NV, Erypo – Janssen-Cilag Pharma GmbH, Erypo FS - Janssen-Cilag GmbH), epoetin beta (NeoRecormon - Roche Registration Limited), epoetin theta (Biopoin - Teva GmbH, Eporatio - Ratiopharm GmbH), epoetin zeta (Retacrit - Hospira UK Limited, Silapo - Stada Arzneimittel AG) and methoxy polyethylene glycol-epoetin beta (Mircera - Roche Registration Limited) should submit a variation within 2 months to amend the product information as described below (new text underlined).

The MAHs should collaboratively distribute a single direct healthcare professional communication (DHPC) according to the text and communication plan agreed with the PRAC and CHMP. The MAH of darbepoetin alfa (Aranesp - Amgen Europe B.V.) should lead the preparation and distribution of the DHPC.

Summary of product characteristics

For all epoetins - 4.4. Special warnings and precautions for use

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with epoetin treatment. More severe cases have been observed with long-acting epoetins.

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, <product name> should be withdrawn immediately and an alternative treatment considered.

If the patient has developed a severe cutaneous skin reaction such as SJS or TEN due to the use of <product name>, treatment with <product name> must not be restarted in this patient at any time.

For all epoetins except darbepoetin alfa and methoxy polyethylene glycol-epoetin beta:

4.8. Undesirable effects - subsection 'Description of selected adverse reactions':

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with epoetin treatment (see section 4.4).

For darbepoetin alfa:

4.8. Undesirable effects – table of ADRs – both for Chronic renal failure patients and for Cancer patients:

Skin and subcutaneous tissue disorders – (frequency not known) - SJS/TEN, erythema multiforme, blistering, skin exfoliation*

Comment under the table: *see section "Description of selected adverse reactions" below and section 4.4

4.8. Undesirable effects – subsection 'Description of selected adverse reactions':

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported (see section 4.4).

Package leaflet

For all epoetins

Section Warnings and precautions - Take special care with <product name>:

Serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with epoetin treatment.

SJS/TEN can appear initially as reddish target-like spots or circular patches often with central blisters on the trunk. Also, ulcers of mouth, throat, nose, genitals and eyes (red and swollen eyes) can occur. These serious skin rashes are often preceded by fever and/or flu-like symptoms. The rashes may progress to widespread peeling of the skin and life-threatening complications.

If you develop a serious rash or another of these skin symptoms, stop taking <product name> and contact your doctor or seek medical attention immediately.

Section Possible side effects

Serious skin rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in association with epoetin treatment. These can appear as reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and can be preceded by fever and flu-like symptoms. Stop using <product name> if you develop these symptoms and contact your doctor or seek medical attention immediately. See also section 2.

1.4. Fulvestrant – Anaphylactic reaction

Authorisation procedure	Centralised
EPITT No	18832
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of adoption	6 July 2017

Recommendation

Having considered the available evidence in EudraVigilance and the already established causal relationship between fulvestrant and hypersensitivity reactions, the PRAC agreed that also anaphylactic reactions should be included in the product information. Therefore, the MAH of fulvestrant-containing products 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

Immune system disorders

Frequency 'Common': Hypersensitivity reactions

Frequency 'Uncommon': Anaphylactic reactions

Package leaflet

4. Possible side effects

You may need immediate medical treatment if you experience any of the following side effects:

• Allergic (hypersensitivity) reactions, including swelling of the face, lips, tongue and/or throat that may be signs of anaphylactic reactions

• …

Uncommon side effects (may affect up to 1 in 100 people)

- …
- Anaphylactic reactions

1.5. Intravenous (IV) fluids containing electrolytes and/or carbohydrates – Hyponatraemia

Authorisation procedure	Non-centralised
EPITT No	18631
PRAC rapporteur(s)	Doris Stenver (DK)
Date of adoption	6 July 2017

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, and the known association of hyponatraemia with the administration of IV fluids containing electrolytes and/or carbohydrates, the PRAC has agreed that the MAH(s) of IV fluids containing electrolytes and/or carbohydrates containing medicinal products should submit a variation within 6 months, to amend the product information according to the below principles. The below wording purpose is guidance and is to be adapted at an individual product level.

The wording below should be adapted at an individual product level and therefore, the type of variation to be submitted should be agreed with the relevant National Competent Authority (NCA) prior to the submission.

Summary of product characteristics (SmPC) for fluids containing glucose

The adjustments are based on the existing SmPC for a glucose 5% IV fluid. Hence, for other glucose containing products in this category (i.e. B05BA03 (carbohydrates) and B05BB02 (electrolytes with carbohydrates)), the SmPC adjustments may need to be adapted and merged into the actual SmPC for the particular product – such that the essence of the required adjustments are preserved.

4.2. Posology and method of administration

Fluid balance, serum glucose, serum sodium and other electrolytes may need to be monitored before and during administration, especially in patients with increased non-osmotic vasopressin release (syndrome of inappropriate antidiuretic hormone secretion, SIADH) and in patients co-medicated with vasopressin agonist drugs due to the risk of hyponatraemia.

Monitoring of serum sodium is particularly important for physiologically hypotonic fluids. <Product name> may become extremely hypotonic after administration due to glucose metabolization in the body (see sections 4.4, 4.5 and 4.8).

4.4. Special warnings and precautions for use

Glucose intravenous infusions are usually isotonic solutions. In the body, however, glucose containing fluids can become extremely physiologically hypotonic due to rapid glucose metabolization (see section 4.2).

Depending on the tonicity of the solution, the volume and rate of infusion and depending on a patient's underlying clinical condition and capability to metabolize glucose, intravenous administration of glucose can cause electrolyte disturbances most importantly hypo- or hyperosmotic hyponatraemia.

Hyponatraemia:

Patients with non-osmotic vasopressin release (e.g. in acute illness, pain, post-operative stress, infections, burns, and CNS diseases), patients with heart-, liver- and kidney diseases and patients exposed to vasopressin agonists (see section 4.5) are at particular risk of acute hyponatraemia upon infusion of hypotonic fluids.

Acute hyponatraemia can lead to acute hyponatraemic encephalopathy (brain oedema) characterized by headache, nausea, seizures, lethargy and vomiting. Patients with brain oedema are at particular risk of severe, irreversible and life-threatening brain injury.

Children, women in the fertile age and patients with reduced cerebral compliance (e.g. meningitis, intracranial bleeding, and cerebral contusion) are at particular risk of the severe and life-threatening brain swelling caused by acute hyponatraemia.

4.5. Interaction with other medicinal products and other forms of interaction

Drugs leading to an increased vasopressin effect
The below listed drugs increase the vasopressin effect, leading to reduced renal electrolyte free water excretion and increase the risk of hospital acquired hyponatraemia following inappropriately balanced treatment with i.v. fluids (see sections 4.2, 4.4 and 4.8).

- Drugs stimulating vasopressin release, e.g.:
  Chlorpropamide, clofibrate, carbamazepine, vincristine, selective serotonin reuptake inhibitors, 3.4-methylenedioxy-N-methamphetamine, ifosfamide, antipsychotics, narcotics
- Drugs potentiating vasopressin action, e.g.:
  Chlorpropamide, NSAIDs, cyclophosphamide
- Vasopressin analogues, e.g.:
  Desmopressin, oxytocin, vasopressin, terlipressin

Other medicinal products increasing the risk of hyponatraemia also include diuretics in general and antiepileptics such as oxcarbazepine.

4.6. Fertility, pregnancy and lactation

<Product name> should be administrated with special caution for pregnant women during labour particularly if administered in combination with oxytocin due to the risk of hyponatraemia (see section

4.4, 4.5 and 4.8).

4.8. Undesirable effects

Tabulated list of adverse reactions		
System Organ Class	Adverse reaction (MedDRA term)	Frequency
Metabolism and nutrition disorders	Hospital Acquired Hyponatraemia**	Not known
Nervous system disorders	Hyponatraemic encephalopathy**	Not known

** Hospital acquired hyponatraemia may cause irreversible brain injury and death due to development of acute hyponatraemic encephalopathy (see sections 4.2 and 4.4).

SmPC for IV fluids without glucose

The adjustments are based on an existing SmPC for a Ringer Lactate i.v. fluid. Hence, for other products in this category (i.e. B05BB01 – electrolytes; hypotonic products), the SmPC adjustments may need to be adapted and merged into the actual SmPC for the particular product – such that the essence of the required adjustments are preserved.

4.2. Posology and method of administration

Fluid balance, serum electrolytes and acid-base balance may need to be monitored before and during administration, with particular attention to serum sodium in patients with increased non-osmotic vasopressin release (syndrome of inappropriate antidiuretic hormone secretion, SIADH) and in patients co-medicated with vasopressin agonist drugs, due to the risk of hospital acquired hyponatraemia (see sections 4.4, 4.5 and 4.8).
Monitoring of serum sodium is particularly important for hypotonic fluids.
<Product name> tonicity: XXX

The infusion rate and volume depend on the age, weight, clinical condition (e.g. burns, surgery, head-injury, infections), and concomitant therapy should be determined by the consulting physician experienced in paediatric intravenous fluid therapy (see sections 4.4. and 4.8).

4.4. Special warnings and precautions for use

High volume infusion must be used under specific monitoring in patients with cardiac or pulmonary failure, and in patients with non-osmotic vasopressin release (including SIADH), due to the risk of hospital-acquired hyponatraemia (see below).

Hyponatraemia
Patients with non-osmotic vasopressin release (e.g. in acute illness, pain, post-operative stress, infections, burns, and CNS diseases), patients with heart-, liver- and kidney diseases and patients exposed to vasopressin agonists (see section 4.5) are at particular risk of acute hyponatraemia upon infusion of hypotonic fluids.

Acute hyponatraemia can lead to acute hyponatraemic encephalopathy (cerebral oedema) characterized by headache, nausea, seizures, lethargy and vomiting. Patients with cerebral oedema are at particular risk of severe, irreversible and life-threatening brain injury.

Children, women in the fertile age and patients with reduced cerebral compliance (e.g. meningitis, intracranial bleeding, cerebral contusion and brain oedema) are at particular risk of the severe and life-threatening brain swelling caused by acute hyponatraemia.

4.5. Interaction with other medicinal products and other forms of interaction

Drugs leading to an increased vasopressin effect
The below listed drugs increase the vasopressin effect, leading to reduced renal electrolyte free water excretion and may increase the risk of hospital acquired hyponatraemia following inappropriately balanced treatment with i.v. fluids (see sections 4.2, 4.4 and 4.8).

- Drugs stimulating vasopressin release include:
  Chlorpropamide, clofibrate, carbamazepine, vincristine, selective serotonin reuptake inhibitors, 3.4-methylenedioxy-N-methamphetamine, ifosfamide, antipsychotics, narcotics
- Drugs potentiating vasopressin action include:
  Chlorpropamide, NSAIDs, cyclophosphamide
- Vasopressin analogues include:
  Desmopressin, oxytocin, vasopressin, terlipressin

Other medicinal products increasing the risk of hyponatraemia also include diuretics in general and antiepileptics such as oxcarbazepine.

4.6. Fertility, pregnancy and lactation

<Product name> should be administrated with special caution for pregnant women during labour particularly as to serum-sodium if administered in combination with oxytocin (see section 4.4, 4.5 and 4.8).

4.8. Undesirable effects

- Hospital acquired hyponatraemia*
- Acute hyponatraemic encephalopathy*

*Hospital acquired hyponatraemia may cause irreversible brain injury and death, due to development of acute hyponatraemic encephalopathy, frequency unknown (see sections 4.2. 4.4, 4.5).

1.6. Prednisolone; prednisone – Induced scleroderma renal crisis

Authorisation procedure	Non-centralised
EPITT No	18888
PRAC rapporteur(s)	Doris Stenver (DK)
Date of adoption	6 July 2017

Recommendation

Having considered the available evidence, including from published literature, the PRAC has agreed that the MAHs of systemic formulations of prednisolone-containing medicinal products and prednisone-containing medicinal products in doses which provide a systemic concentration equivalent to more than 15 mg prednisolone daily should submit a variation within 2 months, to amend the product information as described below (new text underlined) as applicable.

For topical formulations, the systemic absorption of prednisolone-containing medicinal products and prednisone-containing medicinal products is expected to be low. Therefore, systemic concentrations corresponding to more than 15 mg prednisolone daily are unlikely. Action for these drugs is therefore not required.

Summary of product characteristics

4.4. Special warnings and precautions for use

Scleroderma renal crisis

Caution is required in patients with systemic sclerosis because of an increased incidence of (possibly fatal) scleroderma renal crisis with hypertension and decreased urinary output observed with a daily dose of 15 mg or more prednisolone. Blood pressure and renal function (s-creatinine) should therefore be routinely checked. When renal crisis is suspected, blood pressure should be carefully controlled.

4.8. Undesirable effects

Frequency 'unknown': Scleroderma renal crisis*

*see section c)

Scleroderma renal crisis

Amongst the different subpopulations the occurrence of scleroderma renal crisis varies. The highest risk has been reported in patients with diffuse systemic sclerosis. The lowest risk has been reported in patients with limited systemic sclerosis (2%) and juvenile onset systemic sclerosis (1%)

Package leaflet

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

Warnings and precautions

Talk to your doctor before taking <product name>, if you have:

Scleroderma (also known as systemic sclerosis, an autoimmune disorder) because daily doses of 15 mg or more may increase the risk of a serious complication called scleroderma renal crisis. Signs of

scleroderma renal crisis include increased blood pressure and decreased urine production. The doctor may advise that you have your blood pressure and urine regularly checked.

4. Possible side effects

Side effects where the frequency is not known

Scleroderma renal crisis in patients already suffering from scleroderma (an autoimmune disorder). Signs of scleroderma renal crisis include increased blood pressure and decreased urine production.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Ritonavir; lopinavir, ritonavir; levothyroxine	Interaction possibly leading to decreased levothyroxine efficacy and hypothyroidism (18896)	Menno van der Elst (NL)	Supplementary information requested (submission by 27 September 2017)	AbbVie Limited
Tofacitinib	Angioedema (18904)	Sabine Straus (NL)	Supplementary information requested (submission by 27 September 2017)	Pfizer Limited

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Darbepoetin alfa; epoetin alfa; epoetin beta; epoetin theta; epoetin zeta; methoxy polyethylene glycol-epoetin beta	Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (18846)	Valerie Straßmann (DE)	· See section 1.3 · Update the RMP of darbepoetin alfa (Aranesp - Amgen Europe B.V.) · Circulate a Direct Healthcare Professional Communication (DHPC)	Amgen Europe B.V., Medice Arzneimittel Pütter GmbH & Co. KG, Sandoz GmbH, Hexal AG, Janssen-Cilag NV, Janssen-Cilag Pharma GmbH, Janssen-Cilag GmbH, Roche Registration Limited, Teva GmbH, Ratiopharm GmbH, Hospira UK Limited, Stada Arzneimittel AG
Desloratadine; loratadine	Weight increased in children (18906)	Laurence de Fays (BE)	Provide comments on proposed updates to the product information (submission by 24 August 2017)	Merck Sharp & Dohme; Bayer
Enzalutamide	Hepatotoxicity (18754)	Eva Segovia (ES)	Review in next PSUR	Astellas Pharma Europe B.V.
Exenatide	Incorrect use of device associated with (serious) adverse reactions including hyperglycaemia and hypoglycaemia (18688)	Qun-Ying Yue (SE)	No action for MAH	AstraZeneca AB