



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 3-6 July 2017 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. Amoxicillin; amoxicillin, clavulanic acid – Drug reaction with eosinophilia and systemic symptoms (DRESS) (EPITT no 18802)

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)).

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)

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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))

2. Ciprofloxacin; meropenem – Incompatibility leading to possible precipitation when co-administered intravenously (EPITT no 18790)

For ciprofloxacin solutions 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).

For meropenem solutions 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.

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) (EPITT no 18846)

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).

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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.

4. Fulvestrant – Anaphylactic reaction (EPITT no 18832)

Summary of product characteristics

4.8. Undesirable effects

Immune system disorders

Frequency ‘Common’: Hypersensitivity reactions

Frequency ‘Uncommon’: Anaphylactic reactions

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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

5. Intravenous (IV) fluids containing electrolytes and/or carbohydrates – Hyponatraemia (EPITT no 18631)

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 metabolism 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 metabolism (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 administered 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 administered 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).

6. Prednisolone; prednisone – Induced scleroderma renal crisis (EPI TT no 18888)

Medicinal products concerned: 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

For topical formulations, no action is 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.