4 January 2019[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 26-29 November 2018 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. Canagliflozin; dapagliflozin; empagliflozin; ertugliflozin – Fournier's gangrene (EPITT no 19308)

Summary of product characteristics

4.4. Special warnings and precautions for use

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotizing fasciitis. If Fournier's gangrene is suspected, X should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

4.8. Undesirable effects

Infections and infestations

[1] Intended publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.

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Necrotising fasciitis of the perineum (Fournier´s Gangrene)[1]

Frequency: not known

[1] see section 4.4

Package leaflet

2. What you need to know before you take X

Talk to your doctor immediately if you develop a combination of symptoms of pain, tenderness, redness, or swelling of the genitals or the area between the genitals and the anus with fever or feeling generally unwell. These symptoms could be a sign of a rare but serious or even life-threatening infection, called necrotizing fasciitis of the perineum or Fournier's gangrene which destroys the tissue under the skin. Fournier´s gangrene has to be treated immediately.

4. Possible side effects

Necrotising fasciitis of the perineum or Fournier´s gangrene, a serious soft tissue infection of the genitals or the area between the genitals and the anus.

2. Carbimazole; thiamazole – New information on the known risk of birth defects and neonatal disorders in case of exposure during pregnancy (EPITT no 19238)

Carbimazole

Summary of product characteristics

4.4. Special warnings and precautions for use

Women of childbearing potential and pregnancy

Women of childbearing potential have to use effective contraceptive measures during treatment.
The use of carbimazole in pregnant women must be based on the individual benefit/risk assessment. If carbimazole is used during pregnancy, the lowest effective dose without additional administration of thyroid hormones should be administered. Close maternal, foetal and neonatal monitoring is warranted (see section 4.6).

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraceptive measures during treatment (see section 4.4).

Pregnancy

Hyperthyroidism in pregnant women should be adequately treated to prevent serious maternal and foetal complications.

Carbimazole is able to cross the human placenta.

Based on human experience from epidemiological studies and spontaneous reporting, carbimazole is suspected to cause congenital malformations when administered during pregnancy, particularly in the first trimester of pregnancy and at high doses.

Reported malformations include aplasia cutis congenita, craniofacial malformations (choanal atresia; facial dysmorphism), exomphalos, oesophageal atresia, omphalo-mesenteric duct anomaly, and ventricular septal defect.

Carbimazole must only be administered during pregnancy after a strict individual benefit/risk assessment and only at the lowest effective dose without additional administration of thyroid hormones. If carbimazole is used during pregnancy, close maternal, foetal and neonatal monitoring is recommended (see section 4.4).

Package leaflet

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

Warnings and precautions

<Medicinal product> can cause harm to an unborn baby. If you could get pregnant, use reliable contraception from the time you start treatment and during treatment.

Pregnancy

<Medicinal product> can cause harm to an unborn baby.

If you could get pregnant, use reliable contraception from the time you start treatment and during treatment.

If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor straight away. Your treatment with <medicinal product> may need to be continued during pregnancy if the potential benefit outweighs the potential risk to you and your unborn baby.

Thiamazole (synonym: methimazole)

Summary of product characteristics

4.4. Special warnings and precautions for use

Women of childbearing potential and pregnancy

Women of childbearing potential have to use effective contraceptive measures during treatment.
The use of thiamazole in pregnant women must be based on the individual benefit/risk assessment. If thiamazole is used during pregnancy, the lowest effective dose without additional administration of thyroid hormones should be administered. Close maternal, foetal, and neonatal monitoring is warranted (see section 4.6).

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraceptive measures during treatment (see section 4.4).

Pregnancy

Hyperthyroidism in pregnant women should be adequately treated to prevent serious maternal and foetal complications.

Thiamazole is able to cross the human placenta.

Based on human experience from epidemiological studies and spontaneous reporting, thiamazole is suspected to cause congenital malformations when administered during pregnancy, particularly in the first trimester of pregnancy and at high doses.

Reported malformations include aplasia cutis congenita, craniofacial malformations (choanal atresia; facial dysmorphism), exomphalos, oesophageal atresia, omphalo-mesenteric duct anomaly, and ventricular septal defect.

Thiamazole must only be administered during pregnancy after a strict individual benefit/risk assessment and only at the lowest effective dose without additional administration of thyroid hormones. If thiamazole is used during pregnancy, close maternal, foetal and neonatal monitoring is recommended (see section 4.4).

Package leaflet

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

Warnings and precautions

<Medicinal product> can cause harm to an unborn baby. If you could get pregnant, use reliable contraception from the time you start treatment and during treatment.

Pregnancy

<Medicinal product> can cause harm to an unborn baby.

If you could get pregnant, use reliable contraception from the time you start treatment and during treatment.

If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor straight away. Your treatment with <medicinal product> may need to be continued during pregnancy if the potential benefit outweighs the potential risk to you and your unborn baby.

3. Carbimazole; thiamazole – Pancreatitis (EPITT no 19274)

Carbimazole

Summary of product characteristics

4.3. Contraindications

Patients with a history of acute pancreatitis after administration of carbimazole or its active metabolite thiamazole.

4.4. Special warnings and precautions for use

There have been post-marketing reports of acute pancreatitis in patients receiving carbimazole or its active metabolite thiamazole. In case of acute pancreatitis, carbimazole should be discontinued immediately. Carbimazole must not be given to patients with a history of acute pancreatitis after administration of carbimazole or its active metabolite thiamazole. Re-exposure may result in recurrence of acute pancreatitis, with decreased time to onset.

4.8. Undesirable effects

Gastrointestinal disorders

Frequency 'not known': Acute pancreatitis

Package leaflet

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

Do not take <medicinal product>

…if you had inflammation of the pancreas (acute pancreatitis) after administration of carbimazole or thiamazole in the past.

Warnings and precautions

…Tell your doctor straight away if you develop fever or abdominal pain, which may be signs of inflammation of the pancreas (acute pancreatitis). <Product name> may need to be discontinued.

4. Possible side effects

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

…inflammation of the pancreas (acute pancreatitis).

Thiamazole (synonym: methimazole)

Summary of product characteristics

4.3. Contraindications

Patients with a history of acute pancreatitis after administration of thiamazole or its prodrug carbimazole.

4.4. Special warnings and precautions for use

There have been post-marketing reports of acute pancreatitis in patients receiving thiamazole or its prodrug carbimazole. In case of acute pancreatitis, thiamazole should be discontinued immediately. Thiamazole must not be given to patients with a history of acute pancreatitis after administration of thiamazole or its prodrug carbimazole. Re-exposure may result in recurrence of acute pancreatitis, with decreased time to onset.

4.8. Undesirable effects

Gastrointestinal disorders

Frequency 'not known': Acute pancreatitis

Package leaflet

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

Do not take <medicinal product>

…if you had inflammation of the pancreas (acute pancreatitis) after administration of thiamazole or carbimazole in the past…

Warnings and precautions

…Tell your doctor straight away if you develop fever or abdominal pain, which may be signs of inflammation of the pancreas (acute pancreatitis). <Product name> may need to be discontinued.

4. Possible side effects

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

…inflammation of the pancreas (acute pancreatitis).

4. Certolizumab pegol; etanercept; golimumab; infliximab – Lichenoid skin reactions (EPITT no 19128)

Summary of product characteristics

4.8. Undesirable effects

Tabulated list of adverse reactions

Skin and subcutaneous tissue disorders

Frequency 'rare': Lichenoid reactions

Package leaflet

4. Possible side effects

Lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes) with frequency 'rare'

5. Dulaglutide; exenatide; liraglutide – Diabetic ketoacidosis (EPITT no 19237)

TRULICITY

Summary of product characteristics

4.2. Posology and method of administration

Add-on therapy

[...]

The use of Trulicity does not require blood glucose self-monitoring. ~~Self-monitoring may be necessary to adjust the dose of sulphonylurea or insulin.~~ Blood glucose self-monitoring is necessary to adjust the dose of sulphonylurea or insulin, particularly when Trulicity therapy is started and insulin is reduced. A stepwise approach to insulin dose reduction is recommended.

4.4. Special warnings and precautions for use
Dulaglutide is not a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin (see section 4.2).

Package leaflet

2. What you need to know before you use Trulicity

Warnings and precautions

[...]

Trulicity is not an insulin and should therefore not be used as a substitute for insulin.

Other medicines and Trulicity
Tell your doctor, pharmacist or nurse if you are using, have recently used or might use any other medicine. Especially tell your doctor:

[...]

- if you are using insulin, your doctor will tell you how to reduce the dose of insulin and will recommend you to monitor your blood sugar more frequently, in order to avoid hyperglycaemia (high blood sugar) and diabetic ketoacidosis (a complication of diabetes that occurs when the body is unable to break down glucose because there is not enough insulin).

BYETTA

Summary of product characteristics

4.2. Posology and method of administration

[...]

The dose of immediate-release exenatide does not need to be adjusted on a day-by-day basis depending on self-monitored glycaemia. ~~However, blood glucose self-monitoring may become necessary to adjust the dose of sulphonylureas or the dose of basal insulin.~~ Blood glucose self-monitoring is necessary to adjust the dose of sulphonylurea or insulin, particularly when Byetta therapy is started and insulin is reduced. A stepwise approach to insulin dose reduction is recommended.

4.4. Special warnings and precautions for use
Exenatide is not a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin (see section 4.2).

Package leaflet

2. What you need to know before you use Byetta

Warnings and precautions

[…]

Byetta is not an insulin and should therefore not be used as a substitute for insulin.

3. How to use Byetta

[…]

You will **not** need to test your sugar levels on a day-by-day basis to set the dose of Byetta. However, if you are also using a sulphonylurea or an insulin your doctor may tell you to check your blood sugar levels to adjust the dose of sulphonylurea or insulin. If you are using insulin, your doctor will tell you how to reduce the dose of insulin and will recommend you to monitor your blood sugar more frequently, in order to avoid hyperglycaemia (high blood sugar) and diabetic ketoacidosis (a complication of diabetes that occurs when the body is unable to break down glucose because there is not enough insulin).

BYDUREON

Summary of product characteristics

4.2. Posology and method of administration

[…]

The use of prolonged-release exenatide does not require additional self-monitoring. ~~Blood glucose self-monitoring may be necessary to adjust the dose of sulphonylurea.~~ Blood glucose self-monitoring is necessary to adjust the dose of sulphonylurea and of insulin particularly when prolonged-release exenatide therapy is started and insulin is reduced. A stepwise approach to insulin dose reduction is recommended.

4.4. Special warnings and precautions for use
[…]

Prolonged-release exenatide is not a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin (see section 4.2).

Package leaflet

2. What you need to know before you use Bydureon

Warnings and precautions

[…]

Bydureon is not an insulin and should therefore not be used as a substitute for insulin.

Other medicines and Bydureon
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines, particularly:

[…]
- if you are using insulin, your doctor will tell you how to reduce the dose of insulin and will recommend you to monitor your blood sugar more frequently, in order to avoid hyperglycaemia (high blood sugar) and diabetic ketoacidosis (a complication of diabetes that occurs when the body is unable to break down glucose because there is not enough insulin).

VICTOZA

Summary of product characteristics

4.2. Posology and method of administration

[…]

Self-monitoring of blood glucose is not needed in order to adjust the dose of Victoza. ~~However, when initiating treatment with Victoza in combination with a sulfonylurea or insulin, blood glucose self-monitoring may become necessary to adjust the dose of the sulfonylurea or the insulin.~~ Blood glucose self-monitoring is necessary to adjust the dose of sulphonylurea and insulin, particularly when Victoza therapy is started and insulin is reduced. A stepwise approach to insulin dose reduction is recommended.

4.4. Special warnings and precautions for use
[…]

Liraglutide is not a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin (see section 4.2).

Package leaflet

2. What you need to know before you use Victoza

In particular, tell your doctor, pharmacist or nurse if you are using medicines containing any of the following active substances:

[…]

- if you are using insulin, your doctor will tell you how to reduce the dose of insulin and will recommend you to monitor your blood sugar more frequently, in order to avoid hyperglycaemia (high blood sugar) and diabetic ketoacidosis (a complication of diabetes that occurs when the body is unable to break down glucose because there is not enough insulin).

SAXENDA

Summary of product characteristics

4.2. Posology and method of administration

[…]

When initiating Saxenda, consider reducing the dose of concomitantly administered insulin or insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycaemia. Blood glucose self-monitoring is necessary to adjust the dose of insulin or insulin-secretagogues.

4.4. Special warnings and precautions for use

In patients with diabetes mellitus Saxenda must not be used as a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin (see section 4.2).

6. Perindopril – Raynaud's phenomenon (EPITT no 19248)

Summary of product characteristics

4.8. Undesirable effects

Tabulated list of adverse reactions

Vascular disorders

Frequency 'not known': Raynaud's phenomenon

Package leaflet

4. Possible side effects

Frequency not known (cannot be estimated from available data): Discoloration, numbness and pain in fingers or toes (Raynaud's phenomenon).