



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

## PRAC recommendations on signals

Adopted at the 26-29 November 2018 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 26-29 November 2018 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT]<sup>2</sup> 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 (10-13 December 2018) 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.

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<sup>1</sup> Intended publication date. The actual publication date can be checked on the webpage dedicated to [PRAC recommendations on safety signals](#).

<sup>2</sup> 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 information<sup>3</sup>

## 1.1. Canagliflozin; dapagliflozin; empagliflozin; ertugliflozin – Fournier's gangrene

<b>Authorisation procedure</b>	Centralised
<b>EPITT No</b>	19308
<b>PRAC rapporteur(s)</b>	Martin Huber (DE)
<b>Date of adoption</b>	29 November 2018

### Recommendation [see also section 3]

Based on the assessment of the available data sources, the PRAC considered that the most recent data demonstrates a possible causal association between Fournier's gangrene and SGLT-2 inhibitors. Therefore, the PRAC has agreed that the MAHs for the SGLT-2 inhibitors products are to 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 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

###### Necrotising fasciitis of the perineum (Fournier's Gangrene)<sup>1</sup>

Frequency: not known

<sup>1</sup> 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

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

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.

### **1.2. Carbimazole; thiamazole – New information on the known risk of birth defects and neonatal disorders in case of exposure during pregnancy**

<b>Authorisation procedure</b>	Non-centralised
<b>EPITT No</b>	19238
<b>PRAC rapporteur(s)</b>	Martin Huber (DE)
<b>Date of adoption</b>	29 November 2018

#### **Recommendation** [see also section 3]

Based on the assessment of the available data sources, the PRAC considered that data from epidemiological studies and case reports strengthens the evidence that carbimazole/thiamazole can cause congenital malformations when administered during pregnancy. Therefore, the PRAC has agreed that the MAHs for the carbimazole and thiamazole containing products are to submit a variation within 2 months, to amend the product information as described below (new text underlined):

#### **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.

### 1.3. Carbimazole; thiamazole – Pancreatitis

Authorisation procedure	Non-centralised
EPI TT No	19274
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	29 November 2018

#### Recommendation [see also section 3]

Based on the assessment of the available data sources (i.e. literature, EudraVigilance), the PRAC considered that the most recent data demonstrates an association between thiamazole/carbimazole and pancreatitis. Therefore, the PRAC has agreed that the MAHs for the carbimazole or thiamazole (synonym: methimazole) containing products are to submit a variation within 2 months, to amend the product information as described below (new text underlined):

#### 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

The following adverse reaction should be added under the SOC Gastrointestinal disorders with a 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

The following adverse reaction should be added under the SOC Gastrointestinal disorders with a 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).

#### **1.4. Certolizumab pegol; etanercept; golimumab; infliximab – Lichenoid skin reactions**

<b>Authorisation procedure</b>	Centralised
<b>EPITT No</b>	19128
<b>PRAC rapporteur(s)</b>	Ulla Wandel Liminga (SE)
<b>Date of adoption</b>	29 November 2018

#### **Recommendation**

Having considered the available evidence from the cumulative review provided by the MAHs and the known association of TNF inhibitors with skin reactions, the PRAC has agreed that the MAH(s) of certolizumab pegol, etanercept, golimumab and infliximab -containing medicinal 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

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'

#### **1.5. Dulaglutide; exenatide; liraglutide – Diabetic ketoacidosis**

<b>Authorisation procedure</b>	Centralised
<b>EPITT No</b>	19237
<b>PRAC rapporteur(s)</b>	Amelia Cupelli (IT)
<b>Date of adoption</b>	29 November 2018

#### **Recommendation**

Having considered the available evidence from spontaneous cases reported for dulaglutide, exenatide and liraglutide, the PRAC has agreed that the occurrence of diabetic ketoacidosis in a consistent number of cases could be attributed to the abrupt dose reduction or discontinuation from insulin while initiating the GLP-1 receptor agonist resulting in a poor glycaemic control. To provide further guidance for prescribers and patients in adopting a stepwise dose-reduction of insulin and/or close monitoring of blood glucose levels, the PRAC has agreed that the MAH(s) of Trulicity, Byetta, Bydureon, Victoza and Saxenda should submit a variation within 2 months, to amend the product information in Sections 4.2 and 4.4 (and in respective Package leaflet sections) as described below (new text underlined, deleted text ~~strike through~~):

## TRULICITY

### Summary of product characteristics

#### 4.2. Posology and method of administration

##### *Add-on therapy*

[...]

When Trulicity is added to existing metformin and/or pioglitazone therapy, the current dose of metformin and/or pioglitazone can be continued. When Trulicity is added to existing metformin and/or sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy, the current dose of metformin and/or SGLT2i can be continued. When it is added to existing therapy of a sulphonylurea or insulin, a reduction in the dose of sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia (see sections 4.4 and 4.8).

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 should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

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

Talk to your doctor, pharmacist or nurse before using Trulicity if:

[...]

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 other medicines that lower the amount of sugar in your blood, such as insulin or a medicine containing sulphonylurea. Your doctor may want to lower the dose of these other medicines to prevent you from getting low blood sugar levels (hypoglycaemia). Ask your doctor, pharmacist or nurse if you are not sure what your other medicines contain.

- 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

[...]

When immediate-release exenatide is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia (see section 4.4.). When immediate-release exenatide is used in combination with basal insulin, the dose of basal insulin should be evaluated. In patients at increased risk of hypoglycaemia reducing the dose of basal insulin should be considered (see section 4.8).

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 should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

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

Talk to your doctor, pharmacist, or diabetes nurse before using Byetta about the following:

[...]

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 should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

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

Talk to your doctor, pharmacist, or diabetes nurse before using Byetta about the following:

[...]

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

Victoza can be added to existing sulphonylurea or to a combination of metformin and sulphonylurea therapy or insulin. When Victoza is added to sulphonylurea therapy or insulin, a reduction in the dose of sulphonylurea or insulin should be considered to reduce the risk of hypoglycaemia (see section 4.4).

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 sulphonylurea or insulin, blood glucose self-monitoring may become necessary to adjust the dose of the sulphonylurea 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 should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

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:

- Sulfonylurea (such as glimepiride or glibenclamide) or insulin. You may get hypoglycaemia (low blood sugar) when using Victoza together with a sulfonylurea or insulin, as sulfonylureas and insulin increase the risk of hypoglycaemia. When you first start using these medicines together, your doctor may tell you to lower the dose of the sulfonylurea or insulin. Please see section 4 for the warning signs of low blood sugar. If you are also taking a sulfonylurea (such as glimepiride or glibenclamide) or insulin, your doctor may tell you to test your blood sugar levels. This will help your doctor to decide if the dose of the sulfonylurea or insulin needs to be changed.

- 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

Saxenda should not be used in combination with another GLP-1 receptor agonist.

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).

## 1.6. Perindopril – Raynaud's phenomenon

<b>Authorisation procedure</b>	Non-centralised
<b>EPITT No</b>	19248
<b>PRAC rapporteur(s)</b>	Doris Irene Stenver (DK)
<b>Date of adoption</b>	29 November 2018

### Recommendation

Having considered the available evidence on Raynaud's Phenomenon as well as the data submitted by Les Laboratoires Servier (MAH innovator), the PRAC has agreed that the MAHs of perindopril containing medical products and perindopril containing combination products should submit a variation within 3 months, to amend the product information as described below:

#### 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

Like all medicines, this medicine can cause side effects, although not everybody gets them.

[...]

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

## 2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Alectinib	Erythema multiforme (19321)	Patrick Batty (UK)	Assess in the ongoing PSUR procedure (PSUSA/00010581/201807) (submission of the cumulative review by 19 December 2018)	Roche Registration GmbH
Benralizumab	Anaphylactic reaction (19319)	David Benee Olsen (NO)	Assess in the next PSUR (submission by 22 January 2019)	AstraZeneca AB
Clopidogrel; clopidogrel, acetylsalicylic acid	Interaction with boosted antiviral human immunodeficiency virus (HIV) therapy leading to insufficient inhibition of platelet aggregation (19325)	Márcia Silva (PT)	Supplementary information requested (submission by 6 February 2019)	Sanofi Clir SNC
Idelalisib	Arthritis and arthralgia (19312)	Patrick Batty (UK)	Supplementary information requested (submission by 6 February 2019)	Gilead Sciences Ireland UC
Inactivated poliomyelitis vaccine, including combination vaccines	Case reports from outside the EU of immune thrombocytopenic purpura (19336)	Doris Irene Stenver (DK)	Supplementary information requested (submission by 6 February 2019)	Sanofi Pasteur
Ivacaftor; ivacaftor, tezacaftor	Increased blood creatine phosphokinase (CPK) (19316)	Rhea Fitzgerald (IE)	Supplementary information requested (submission by 6 February 2019)	Vertex Pharmaceuticals (Europe) Ltd.
Natalizumab	Human papillomavirus (HPV) infection and complications (19329)	Brigitte Keller Stanislawski (DE)	Assess in the ongoing PSUR procedure (submission by 16 January 2019)	Biogen Netherlands B.V.

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Selective serotonin reuptake inhibitors (SSRI): citalopram; escitalopram	Drug interaction with fluconazole (19327)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 6 February 2019)	H. Lundbeck A/S
Sorafenib	Acute generalised exanthous pustulosis (AGEP) (18109)	Annika Folin (SE)	Supplementary information requested (submission by 6 February 2019)	Bayer AG
Trastuzumab emtansine	Sepsis (19326)	Doris Irene Stenver (DK)	Assess in the next PSUR (submission by 2 May 2019)	Roche Registration GmbH

### 3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Canagliflozin; dapagliflozin; empagliflozin; ertugliflozin	Fournier's gangrene (19308)	Martin Huber (DE)	<ul style="list-style-type: none"> <li>• See section 1.1</li> <li>• Circulate a Direct Healthcare Professional Communication (DHPC)</li> <li>• Routine pharmacovigilance</li> </ul>	Janssen-Cilag International NV; AstraZeneca AB; Boehringer Ingelheim International GmbH; Merck Sharp & Dohme B.V.
Carbimazole; thiamazole	New information on the known risk of birth defects and neonatal disorders in case of exposure during pregnancy (19238)	Martin Huber (DE)	<ul style="list-style-type: none"> <li>• See section 1.2</li> <li>• Circulate a Direct Healthcare Professional Communication (DHPC)</li> </ul>	MAHs of carbimazole or thiamazole (synonym: methimazole) containing products
Carbimazole; thiamazole	Pancreatitis (19274)	Martin Huber (DE)	<ul style="list-style-type: none"> <li>• See section 1.3</li> <li>• Circulate a Direct Healthcare Professional Communication (DHPC)</li> </ul>	MAHs of carbimazole or thiamazole (synonym: methimazole) containing products

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Dasabuvir; ombitasvir, paritaprevir, ritonavir	Interstitial lung disease (19257)	Maria del Pilar Rayón (ES)	Routine pharmacovigilance	AbbVie Limited
Olmesartan	Autoimmune hepatitis (19258)	Martin Huber (DE)	Routine pharmacovigilance	MAHs of olmesartan containing products
Propranolol	Increased risk of Parkinson's disease (19223)	Karen Pernille Harg (NO)	PSUR submission frequency amended to 3-yearly PSURs (next DLP set to 30/06/2021)	MAHs of propranolol containing products
Ranibizumab	Angioedema (19245)	Ulla Wändel Liminga (SE)	Routine pharmacovigilance	Novartis Europharm Ltd
Vemurafenib	Cardiac failure (19268)	Annika Folin (SE)	Routine pharmacovigilance	Roche Registration GmbH
Vascular endothelial growth factor (VEGF) inhibitors <sup>4</sup>	Artery dissections and aneurysms (19330)	Annika Folin (SE)	No action at this stage	Not applicable

<sup>4</sup> Aflibercept; axitinib; bevacizumab; cabozantinib; lenvatinib; nintedanib; pazopanib; pegaptanib; ponatinib; ramucirumab; ranibizumab; sorafenib; sunitinib; tivozanib; vandetanib