25 January 2018
EMA/PRAC/8429/2018 Corr[1]
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 8-11 January 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 8-11 January 2018 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][2] 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 (22-25 January 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.

[1] A minor amendment was implemented for the pemetrexed signal on 15 February 2018 (see page 7).
[2] 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[3]

1.1. Dulaglutide – Gastrointestinal stenosis and obstruction

Authorisation procedure	Centralised
EPITT No	18931
PRAC rapporteur(s)	Carmela Macchiarulo (IT)
Date of adoption	11 January 2018

Recommendation

Having considered the available evidence in EudraVigilance, including the data submitted by the MAH, the PRAC has agreed that the MAH of Trulicity (Elli Lilly) 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

Gastrointestinal disorders

Frequency 'not known': Non-mechanical intestinal obstruction

Package leaflet

4. Possible side effects

Frequency 'not known'

Bowel obstruction - a severe form of constipation with additional symptoms such as stomach ache, bloating or vomiting

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

1.2. Methotrexate – Pulmonary alveolar haemorrhage

Authorisation procedure	Centralised and non-centralised
EPITT No	18850
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	11 January 2018

Recommendation

1.2.1. For methotrexate-containing medicinal products with non-oncologic indications

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the MAH(s) of **methotrexate-containing medicinal products with non-oncologic indications** should submit a variation within 2 months, to amend the product information as described below (the wording of the centrally authorised methotrexate product Nordimet® is taken as the basis, new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

Assessment of respiratory system
Questioning the patient with regard to possible pulmonary dysfunctions, if necessary lung function test. Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough), thoracic pain and fever for which patients should be monitored at each follow-up visit. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.

In addition, pulmonary alveolar haemorrhage has been reported with methotrexate used in rheumatologic and related indications. This event may also be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis.

4.8. Undesirable effects

Respiratory, thoracic and mediastinal disorders

Not known: Epistaxis, Pulmonary alveolar haemorrhage

Package leaflet

2. What you need to know before you take [MTX]

Warnings and precautions

Acute bleeding from the lungs in patients with underlying rheumatologic disease has been reported with methotrexate. If you experience symptoms of spitting or coughing up blood you should contact your doctor immediately.

4. Possible side effects

Serious side effects

If you develop any of the following side effects, contact your doctor immediately:

- inflammation of the lungs (symptoms may be general illness, dry, irritating cough, shortness of breath, breathlessness at rest, chest pain, or fever)

- spitting or coughing blood

The following side effects have also been reported:

Frequency not known (cannot be estimated from the available data): bleeding from the lungs

1.2.2. For methotrexate-containing medicinal products with oncologic indications

Having considered the available evidence in EudraVigilance and in the literature in the oncologic indication, the PRAC has agreed that the MAH(s) of **methotrexate-containing medicinal products with oncologic indications** should 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

Respiratory system
Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough), thoracic pain and fever for which patients should be monitored at each follow-up visit. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.

In addition, pulmonary alveolar haemorrhage has been reported with methotrexate used in rheumatologic and related indications. This event may also be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis.

Package leaflet

2. What you need to know before you take [MTX]

Warnings and precautions

Acute bleeding from the lungs in patients with underlying rheumatologic disease has been reported with methotrexate.

1.2.3. For methotrexate-containing medicinal products with both non-oncologic and oncologic indications

Having considered the available evidence in EudraVigilance and in the literature in the oncologic indication, the PRAC has agreed that the MAH(s) of **methotrexate-containing medicinal products with both non-oncologic and oncologic indications** should 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

Respiratory system
Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough), thoracic pain and fever for which patients should be monitored at each follow-up visit. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.

In addition, pulmonary alveolar haemorrhage has been reported with methotrexate used in rheumatologic and related indications. This event may also be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis.

4.8. Undesirable effects

Respiratory, thoracic and mediastinal disorders

Not known: Epistaxis, Pulmonary alveolar haemorrhage*

*(has been reported for methotrexate used in rheumatologic and related indications)

Package leaflet

2. What you need to know before you take [MTX]

Warnings and precautions

Acute bleeding from the lungs in patients with underlying rheumatologic disease has been reported with methotrexate. If you experience symptoms of spitting or coughing up blood you should contact your doctor immediately.

4. Possible side effects

Serious side effects

If you develop any of the following side effects, contact your doctor immediately:

- inflammation of the lungs (symptoms may be general illness, dry, irritating cough, shortness of breath, breathlessness at rest, chest pain, or fever)

- spitting or coughing blood*

*(has been reported for methotrexate used in patients with underlying rheumatologic disease)

The following side effects have also been reported:

Frequency not known (cannot be estimated from the available data): bleeding from the lungs*

*(has been reported for methotrexate used in patients with underlying rheumatologic disease).

1.3. Pemetrexed – Nephrogenic diabetes insipidus

Authorisation procedure	Centralised
EPITT No	18930
PRAC rapporteur(s)	Ghania Chamouni (FR)
Date of adoption	11 January 2018

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the MAHs of pemetrexed-containing products[4] should 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

Serious renal events, including acute renal failure, have been reported with pemetrexed alone or in association with other chemotherapeutic agents. Many of the patients in whom these occurred had underlying risk factors for the development of renal events including dehydration or pre-existing hypertension or diabetes. Nephrogenic diabetes insipidus and renal tubular necrosis were also reported in post marketing setting with pemetrexed alone or with other chemotherapeutic agents. Most of these events resolved after pemetrexed withdrawal. Patients should be regularly monitored for acute tubular necrosis, decreased renal function and signs and symptoms of nephrogenic diabetes insipidus (e.g. hypernatraemia).

4.8. Undesirable effects

Uncommon cases of acute renal failure have been reported with pemetrexed alone or in association with other chemotherapeutic agents (see section 4.4). Nephrogenic diabetes insipidus and renal tubular necrosis have been reported in post marketing setting with an unknown frequency.

Package leaflet

4. Possible side effects

Not known: frequency cannot be estimated from the available data

Increased urine output

Thirst and increased water consumption

Hypernatraemia – increased sodium in blood

No modification of the RMP is advised.

[4] Scope extended to all MAHs of pemetrexed-containing products (amended on 15 February 2018)

1.4. Sodium-containing effervescent, dispersible and soluble medicines – Cardiovascular events[5]

Authorisation procedure	Centralised and non-centralised
EPITT No	17931
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	10 April 2015

In April 2015 the PRAC discussed the signal of cardiovascular events with sodium-containing effervescent, dispersible and soluble medicines (see pages 6-9 of the document summarising the 7-10 April 2015 PRAC recommendations on signals). The PRAC agreed that following publication of the revised excipient guideline the MAHs should update their labelling at the next regulatory opportunity or within 12 months from the publication.

As the revision of the excipient guideline was published in October 2017, the concerned MAHs are reminded to update their labelling by 9 October 2018. This guideline can be found on the webpage on excipients labelling.

[5] No translation is available for this signal.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adalimumab	Lichenoid keratosis (19128)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 15 March 2018)	AbbVie Limited
Apixaban	Tubulointerstitial nephritis (19127)	Menno van der Elst (NL)	Supplementary information requested (submission by 15 March 2018)	Bristol-Myers Squibb / Pfizer EEIG
Apixaban; edoxaban	Drug interaction between apixaban or edoxaban and selective serotonin reuptake inhibitors and/or serotonin reuptake inhibitors leading to increased risk of bleeding (19139)	Julie Williams (UK)	Supplementary information requested (submission by 15 March 2018)	Bristol-Myers Squibb / Pfizer EEIG; Daiichi Sankyo Europe GmbH
Concentrate of proteolytic enzymes enriched in bromelain	Haemorrhage (19133)	Valerie Strassman n (DE)	Assess in the next PSUR (submission by 25 February 2018)	MediWound Germany GmbH
Lenalidomide	Progressive multifocal leukoencephalopathy (PML)	Ghania Chamouni (FR)	Supplementary information requested (submission by 15 March 2018)	MAHs of lenalidomide containing products
Pembrolizumab	Aseptic meningitis (19115)	Sabine Straus (NL)	Supplementary information requested (submission by 15 March 2018)	Merck Sharp & Dohme Limited

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adalimumab; infliximab	Risk of lymphoma in patients with inflammatory bowel disease (19121)	Ulla Wändel Liminga (SE)	No action at this stage	Not applicable
Hormonal contraceptives	Known association between breast cancer and hormonal contraceptives following a recent publication (19143)	Menno van der Elst (NL)	No action at this stage	Not applicable
Hormonal contraceptives	Suicidality with hormonal contraceptives following a recent publication (19144)	Doris Stenver (DK)	No action at this stage	Not applicable
Hydrochlorothiazide	Skin cancer (19138)	Kirsti Villikka (FI)	No action at this stage	Not applicable
Megestrol; vitamin K antagonists (acenocoumarol, fluindione, phenindione, phenprocoumon, warfarin)	Drug interaction leading to elevated international normalised ratio (INR)/ haemorrhage with megestrol and vitamin K antagonists (18910)	Almath Spooner (IE)	Routine pharmacovigilance	MAHs for megestrol and vitamin K antagonists