1 April 2016
EMA/PRAC/135876/2016
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the PRAC meeting of 14-17 March 2016

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 14-17 March 2016 (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 (29 March-1 April 2016) 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.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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. Axitinib – Nephrotic syndrome

Authorisation procedure	Centralised
EPITT No	18484
PRAC rapporteur(s)	Ingebjørg Buajordet (NO)
Date of adoption	17 March 2016

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that Pfizer, the MAH of Inlyta (axitinib) medicinal product, should submit a variation within 2 months, to amend the section 4.4 of the SPC as described below (new text underlined). The MAH should continue to monitor nephrotic syndrome via routine pharmacovigilance.

Summary of Product Characteristics

Section 4.4

Proteinuria

In clinical studies with axitinib, proteinuria, including that of Grade 3 and 4 severity, was reported (see section 4.8).

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with axitinib is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt axitinib treatment (see section 4.2). Axitinib should be discontinued if the patient develops nephrotic syndrome.

Package Leaflet (PL)

No changes to the PL are needed.

[2] 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. Mercaptopurine; azathioprine – Lymphoproliferative disorders

Authorisation procedure	Centralised and non-centralised
EPITT No	18503
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of adoption	17 March 2016

Recommendation

Having considered the available evidence from spontaneous reports and the literature, the PRAC has agreed that the MAH(s) of mercaptopurine and azathioprine containing medicinal products should submit a variation within 2 months to amend the product information in order to incorporate warnings related to lymphoproliferative disorders and macrophage activation syndrome.

Moreover and considering the potential for carcinogenicity of these products, the PRAC agreed to include information about other malignancies in the product information for mercaptopurine in line with the information already included for azathioprine (pro-drug of mercaptopurine).

Furthermore, the MAH's proposal that *in patients on multiple immunosuppressants, EBV-VCA serology should be ascertained before and during immunosuppressive therapy and careful monitoring with EBV-PCR is recommended*, is not supported. The reasons are that it is unclear what the results of such screening would lead to, and how well it would predict the potential risk.

The product information should include the text as described below:

Summary of Product Characteristics (mercaptopurine and azathioprine):

Section 4.4 Special warnings and precautions for use

Mutagenicity and carcinogenicity/Carcinogenicity

Patients receiving immunosuppressive therapy, including <*azathioprine*> <*mercaptopurine*> are at an increased risk of developing lymphoproliferative disorders and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ. The increased risk appears to be related to the degree and duration of immunosuppression. It has been reported that discontinuation of immunosuppression may provide partial regression of the lymphoproliferative disorder.

A treatment regimen containing multiple immunosuppressants (including thiopurines) should therefore be used with caution as this could lead to lymphoproliferative disorders, some with reported fatalities. A combination of multiple immunosuppressants, given concomitantly increases the risk of Epstein-Barr virus (EBV)-associated lymphoproliferative disorders.

Summary of Product Characteristics (mercaptopurine)

Section 4.4 Special warnings and precautions for use

Macrophage activation syndrome.

Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with autoimmune conditions, in particular with inflammatory bowel disease (IBD) (unlicensed

indication), and there could potentially be an increased susceptibility for developing the condition with the use of mercaptopurine. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible, and treatment with mercaptopurine should be discontinued. Physicians should be attentive to symptoms of infection such as EBV and cytomegalovirus (CMV), as these are known triggers for MAS.

Summary of Product Characteristics (azathioprine)

Section 4.4 Special warnings and precautions for use

Macrophage activation syndrome.

Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with autoimmune conditions, in particular with inflammatory bowel disease (IBD), and there could potentially be an increased susceptibility for developing the condition with the use of azathioprine. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible, and treatment with azathioprine should be discontinued. Physicians should be attentive to symptoms of infection such as EBV and cytomegalovirus (CMV), as these are known triggers for MAS.

Summary of Product Characteristics (mercaptopurine and azathioprine):

Section 4.8 Undesirable effects

Neoplasms benign and malignant (including cysts and polyps)

Rare: neoplasms including lymphoproliferative disorders, skin cancers (melanomas and non-melanomas), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ…(see section 4.4).

Package leaflet (mercaptopurine and azathioprine)

2. What you need to know before you <take> <use> X

Warnings and precautions

Talk to your doctor <or> <pharmacist> <or nurse> before <taking> <using> X

If you are receiving immunosuppressive therapy, taking <X> could put you at greater risk of:

- tumours, including skin cancer. Therefore, when taking <X>, avoid excessive exposure to sunlight, wear protective clothing and use protective sunscreen with a high protection factor.
- lymphoproliferative disorders
    - treatment with <X> increases your risk of getting a type of cancer called lymphoproliferative disorder. With treatment regimen containing multiple immunosuppressants (including thiopurines), this may lead to death.
    - A combination of multiple immunosuppressants, given concomitantly increases the risk of disorders of the lymph system due to a viral infection (Epstein-Barr virus (EBV)-associated lymphoproliferative disorders).

Taking <X> could put you at greater risk of:

- developing a serious condition called Macrophage Activation Syndrome (excessive activation of white blood cells associated with inflammation), which usually occurs in people who have certain types of arthritis

4. Possible side effects

Other side effects include:

Rare (affects less than 1 in 1,000 people)

- various types of cancers including blood, lymph and skin cancers

1.3. Tigecycline – Hypofibrinogenaemia

Authorisation procedure	Centralised
EPITT No	18479
PRAC rapporteur(s)	Miguel A. Maciá (ES)
Date of adoption	17 March 2016

Recommendation

Having considered the available evidence from post-marketing cases and the literature, and the data submitted by the MAH, the PRAC has agreed that the MAH of Tygacil (Pfizer Limited) should submit within 2 months a variation to update the product information as described below (new text underlined).

Summary of Product Characteristics

4.8 Undesirable effects

Tabulated list of adverse reactions

Blood and lymphatic system disorders

Frequency not known (cannot be estimated from the available data): <u>hypofibrinogenaemia</u>

Package leaflet

4. Possible side effects

Not known side effects are (frequency cannot be estimated from the available data):

- <u>Low fibrinogen levels in the blood (a protein involved in blood clotting)</u>

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Ferrous sulphate	Mouth ulceration (18623)	Leonor Chambel (PT)	Supplementary information requested (submission by 02/05/2016)	Wörwag Pharma GmBH & CO. KG; Teva GmBH; Teofarma S.R.L.; Pierre Fabre, Meda pharma; Egis Pharmaceuticals PLC; Novartis; ACO HUD NORDIC AB
Loratadine	QT prolongation and Torsade de Pointe (18576)	Veerle Verlinden (BE)	Assess in the next PSUR (submission by 03/05/2017)	Bayer
Propofol	Diabetes insipidus (18622)	Kristin T. Kvande (NO)	Supplementary information requested (submission by 02/05/2016)	AstraZeneca
Proton pump inhibitors (PPIs): dexlansoprazole; esomeprazole; lansoprazole; omeprazole ; pantoprazole; rabeprazole	Elevated circulating levels of chromogranin A (18614)	Rafe Suvarna (UK)	Supplementary information requested (submission by 02/05/2016)	AstraZeneca; Janssen-Cilag; Takeda
Tramadol; tramadol, paracetamol	Hyponatraemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) (18471)	Julie Williams (UK)	Supplementary information requested (submission by 02/05/2016)	Grünenthal

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Human normal immunoglobulin	Posterior reversible encephalopathy syndrome (PRES) (18512)	Brigitte Keller-Stanislawski (DE)	Monitor in PSUR	MAHs of intravenous immunoglobulins
Intravenous fluids containing electrolytes and/or carbohydrates	Hyponatremia (18631)	Doris Stenver (DK)	No action for MAH	Not applicable
Recombinant Factor VIII: antihemophilic factor (recombinant); moroctocog alfa; octocog alfa	Inhibitor development in previously untreated patients (18134)	Brigitte Keller-Stanislawski (DE)	No action at this stage	Bayer Pharma AG, Baxter AG, Pfizer Limited, various