



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 14-17 March 2016 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).

1. Axitinib (INLYTA) – Nephrotic syndrome (EPITT no 18484)

New text to be added to the product information is underlined. Current text to be deleted is ~~struck through~~.

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. Mercaptopurine (XALUPRINE); azathioprine – Lymphoproliferative disorders (EPITT no 18503)

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

3. Tigecycline (TYGACIL) – Hypofibrinogenaemia (EPITT no 18479)

New text to be added to the product information is underlined. Current text to be deleted is ~~struck through~~.

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): hypofibrinogenaemia

Package leaflet

4. Possible side effects

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

- Low fibrinogen levels in the blood (a protein involved in blood clotting)