



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

7 January 2025¹
EMA/PRAC/537838/2024
Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 25-28 November 2024 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 on the webpage for [PRAC recommendations on safety signals](#) (in English only).

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

1. Azathioprine – Non-cirrhotic portal hypertension / portosinusoidal vascular disease (EPITT no 20091)

Summary of product characteristics (SmPC)

In case the SmPC already includes a similar or stricter wording regarding liver damage, the similar or stricter advice remains valid and should remain. If the SmPC contains statements indicating hepatic damage is primarily described in transplant patients, these statements should be deleted.

4.4 Special warnings and precautions for use

A warning should be amended/added as follows:

Monitoring

[...]

Azathioprine is hepatotoxic and liver function tests should be routinely monitored during treatment. More frequent monitoring may be advisable in those with pre-existing liver disease or receiving other potentially hepatotoxic therapy. Cases of non-cirrhotic portal hypertension/portosinusoidal vascular disease have been reported. Early clinical signs include liver enzyme abnormalities, mild jaundice, thrombocytopenia, and splenomegaly (see section 4.8). The patient should be informed about the

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



symptoms of liver injury and advised to contact their doctor immediately if these occur ~~instructed to discontinue azathioprine immediately if jaundice becomes apparent.~~

4.8. Undesirable effects

Hepatobiliary disorders

Frequency “Not known”:

Non-cirrhotic portal hypertension, portosinusoidal vascular disease

Description of selected adverse reactions

Hepatobiliary disorders

[...]

Rare, but life-threatening hepatic damage associated with chronic administration of azathioprine has been described ~~primarily in transplant patients~~. Histological findings include sinusoidal dilatation, peliosis hepatis, veno-occlusive disease and nodular regenerative hyperplasia. In some cases, withdrawal of azathioprine has resulted in either temporary or permanent improvement in liver histology and the symptoms.

Package leaflet

In case the package leaflet already includes a similar or stricter wording regarding liver damage, the similar or stricter advice remains valid and should remain. If the package leaflet contains statements indicating liver damage is primarily described in transplant patients, these statements should be deleted.

2. What you need to know before you take [product name]

Warning and precautions

Liver damage

Treatment with [product name] may affect the liver and your doctor will monitor your liver function regularly. Tell your doctor if you experience symptoms of liver damage (see section 4 “Possible side effects”).

4. Possible side effects

If you get any of the following serious side effects, talk to your doctor or go to hospital immediately:

[...]

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

Severe liver damage which can be life threatening, especially in ~~transplant~~ patients who receive long-term treatment (like liver injury, non-cirrhotic portal hypertension, portosinusoidal vascular disease). Tell your doctor if you experience any of the following symptoms: yellowing of the skin and the whites of the eyes (jaundice), bruising easily, abdominal discomfort, loss of appetite, fatigue, nausea, or vomiting.

In case the adverse event is already listed in the package leaflet with another frequency, the existing frequency should be maintained.

2. Nitric oxide – Pulmonary oedema in patients with veno-occlusive disease (EPITT no 20086)

Summary of product characteristics

4.4 Special warnings and precautions for use

Pulmonary veno-occlusive disease

Cases of life-threatening pulmonary oedema have been reported with nitric oxide when used in patients with pulmonary veno-occlusive disease. Therefore, the possibility of a veno-occlusive disease should be carefully evaluated if signs of pulmonary oedema occur following the administration of nitric oxide to patients with pulmonary hypertension. If confirmed, treatment is to be discontinued.

Package leaflet

2. What you need to know before you take [product name]

Warnings and precautions

Cases of fluid retention in the lungs have been reported with nitric oxide in patients with disease due to a blocked or narrow vein in the lungs. If you (as a patient) or your child (as a patient) develops shortness of breath or difficulty breathing, contact your doctor immediately.

3. Risperidone oral solution – Medication errors associated with accidental overdoses in children and adolescents treated with risperidone 1 mg/mL oral solution (EPITT no 20085)

Taking into account the already existing wording in some nationally authorised products, the text may need to be adapted by marketing authorisation holders to individual products.

Package leaflet

3. How to take [product name]

Method of administration

FOR ORAL USE

The solution comes with a <dosing device, i.e. pipette or syringe>. Use only the <dosing device> delivered with this medicine for measuring the dose prescribed by the physician. This should be used to help you measure the exact amount dose of medicine you need. Pay attention when measuring a small dose, for example for 0.25 mg, measure 0.25 ml (a quarter millilitre); for 0.5 mg, measure 0.5 ml (half a millilitre).

Follow these steps:

...

7. Rinse the <dosing device, i.e. pipette or syringe> with some water and let it air dry.