



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2015
EMA/PRAC/590265/2015
Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 7-10 September 2015 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).

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

1. Bisphosphonates (alendronic acid; alendronic acid, colecalciferol; clodronic acid; etidronic acid; ibandronic; neridronic acid; pamidronic acid; risedronic acid; tiludronic acid; zoledronic acid) – Osteonecrosis of the external auditory canal (EPITT no 18256)

Summary of Product Characteristics

Section 4.4

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

Section 4.8

Very rare: Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction).



Package Leaflet

Section 4. Possible side effects

Very rare

- Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.

2. Leflunomide – Pulmonary hypertension (EPITT no 18221)

Summary of Product Characteristics

Section 4.4 - Special warnings and precautions for use:

Respiratory reactions

Interstitial lung disease, as well as rare cases of pulmonary hypertension ~~has~~ have been reported during treatment with leflunomide (see section 4.8). The risk of ~~its~~ their occurrence ~~is~~ can be increased in patients with a history of interstitial lung disease. Interstitial lung disease is a potentially fatal disorder, which may occur acutely during therapy. Pulmonary symptoms, such as cough and dyspnoea, may be a reason for discontinuation of the therapy and for further investigation, as appropriate.

Section 4.8 – Undesirable effects:

Respiratory, thoracic and mediastinal disorders

[...]

Frequency 'not known': pulmonary hypertension

Package Leaflet

Section 4. Possible side effects

Tell your doctor **immediately** if you experience:

[...]

- **a cough** or **breathing problems** as these may indicate ~~inflammation~~ problems of the lung (interstitial lung disease or pulmonary hypertension);

[...]

Other side effects such as kidney failure, a decrease in the levels of uric acid in your blood, pulmonary hypertension, male infertility [...] may also occur with an unknown frequency.

3. Thioctic acid – Insulin autoimmune syndrome (EPITT no 18406)

Summary of Products Characteristics

Section 4.4 - Special warnings and precautions for use:

Cases of Insulin Autoimmune Syndrome (IAS) have been reported during treatment with thioctic acid. Patients with human leukocyte antigen genotype such as HLA-DRB1*04:06 and HLA-DRB1*04:03 alleles, are more susceptible to develop IAS when treated with thioctic acid. HLA-DRB1*04:03 allele (susceptibility to IAS odds ratio: 1.6) is especially found in Caucasians, with a higher prevalence in southern than in northern Europe and HLA-DRB1*04:06 allele (susceptibility to IAS odds ratio: 56.6) is especially found in Japanese and Korean patients.

IAS should be considered in the differential diagnosis of spontaneous hypoglycaemia in patients using thioctic acid (see section 4.8).

Section 4.8 - Undesirable effects:

Immune system disorders

Frequency unknown: insulin autoimmune syndrome (see section 4.4)

Package Leaflet

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

Patients with a certain human leukocyte antigen genotype (which is more frequent in Japanese and Korean patients, but is also found in Caucasians) are more prone to development of insulin autoimmune syndrome (disorder of the blood glucose regulating hormones with pronounced lowering of blood sugar levels) when treated with thioctic acid.

Section 4. Possible side effects:

Frequency unknown: Disorder of the blood glucose regulating hormones with pronounced lowering of blood sugar levels (insulin autoimmune syndrome).

4. Trabectedin – Capillary leak syndrome (EPITT no 18115)

Summary of Product Characteristics

Section 4.8 – Undesirable effects

Frequency 'uncommon': Cases of suspected capillary leak syndrome have been reported with trabectedin.