25 November 2024[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 28-31 October 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. Angiotensin II receptor blockers (ARBs): azilsartan; candesartan; eprosartan; irbesartan; losartan; olmesartan; telmisartan; valsartan (single ingredient and fixed dose combinations) – Intestinal angioedema (EPITT no 20104)

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.

Summary of product characteristics

4.4. Special warnings and precautions for use

For olmesartan, irbesartan, valsartan, losartan and candesartan:

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, [including <INN>] (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, <INN> should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

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

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For azilsartan, eprosartan and telmisartan:

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, <INN> should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

4.8. Undesirable effects

For olmesartan, irbesartan, valsartan, losartan, and candesartan: addition within the table of adverse reactions for the respective ARB. For losartan, olmesartan and irbesartan the frequency should be "rare". For valsartan and candesartan, the frequency should be "very rare":

Gastrointestinal disorders

Intestinal angioedema

For azilsartan, eprosartan and telmisartan:

Description of selected adverse reactions:

Cases of intestinal angioedema have been reported after the use of angiotensin II receptor antagonists (see section 4.4).

Package leaflet

For all ARBs (olmesartan, azilsartan, candesartan, eprosartan, irbesartan, valsartan, losartan and telmisartan):

2. What you need to know before you take <product name>

Warnings and precautions

Talk to your doctor if you experience abdominal pain, nausea, vomiting or diarrhoea after taking <product name>. Your doctor will decide on further treatment. Do not stop taking <product name> on your own.

4. Possible side effects

For olmesartan, irbesartan, valsartan, losartan and candesartan addition within the table of adverse reactions for the respective ARB. For losartan, olmesartan and irbesartan the frequency should be "rare". For valsartan and candesartan, the frequency should be "very rare":

Intestinal angioedema: a swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting and diarrhoea

For azilsartan, eprosartan and telmisartan:

Frequency 'not known': Intestinal angioedema: a swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting, and diarrhoea has been reported after the use of similar products.

2. Paracetamol (single ingredient and fixed dose combinations) – High anion gap metabolic acidosis (HAGMA) due to pyroglutamate acidosis (EPITT no 20105)

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.

Summary of product characteristics

4.4. Special warnings and precautions for use

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported ~~Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly~~ in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. ~~as well as those using maximum daily doses of paracetamol.~~ If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring~~, including measurement of urinary 5-oxoproline,~~ is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

4.5. Interaction with other medicinal products and other forms of interaction

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4)

4.8. Undesirable effects

Metabolism and nutrition disorders

High anion gap metabolic acidosis with frequency "Not known" (cannot be estimated from the available data)

Description of selected adverse reactions

High anion gap metabolic acidosis

Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Package leaflet

2. What you need to know before you take <product name>

Warnings and precautions

During treatment with <product name>, tell your doctor straight away if:

[…]

If you have severe illnesses, including severe renal impairment or sepsis (when bacteria and their toxins circulate in the blood leading to organ damage), or you suffer from malnutrition, chronic alcoholism or if you are also taking flucloxacillin (an antibiotic). A serious condition called metabolic acidosis (a blood and fluid abnormality) has been reported in patients in these situations when paracetamol is used at regular doses for a prolonged period or when paracetamol is taken together with flucloxacillin. Symptoms of metabolic acidosis may include: serious breathing difficulties with deep rapid breathing, drowsiness, feeling sick (nausea) and being sick (vomiting).

Other medicines and paracetamol

Please inform your doctor or pharmacist if you are taking:

- flucloxacillin (antibiotic), due to a serious risk of blood and fluid abnormality (called metabolic acidosis) that must have urgent treatment (see section 2).~~, and which may occur particularly in case of patients with severe illness, including severe renal impairment, sepsis (when bacteria and their toxins circulate in the blood leading to organ damage), malnutrition, chronic alcoholism, or when and if the maximum daily doses of paracetamol are is used for a prolonged period.~~

4. Possible side effects

Frequency "Not known" (frequency cannot be estimated from the available data): A serious condition that can make blood more acidic (called metabolic acidosis), in patients with severe illness using paracetamol (see section 2)