

Changes to the Product information as approved by the CHMP on 13 October 2016, pending endorsement by the European Commission

Annex III

Amendments to relevant sections of the Product Information

Note:

These amendments to the relevant sections of the Product Information are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

Amendments to relevant sections of the Product Information

The existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below.

A. Summary of Product Characteristics

4.2 Posology and method of administration

[This section should be revised as follows:]

For products containing metformin as single agent:

Posology

[...]

Adults with normal renal function (GFR ≥ 90 mL/min)

[...]

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

GFR mL/min	Total maximum daily dose (to be divided into 2-3 daily doses)	Additional considerations
60-89	3000 mg	Dose reduction may be considered in relation to declining renal function.
45-59	2000 mg	Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose.
30-44	1000 mg	
<30	-	Metformin is contraindicated.

[...]

[The dosing table above should be adapted for extended-release products containing metformin as single agent as follows:

- The total maximum daily dose for patients with GFR 60-89 mL/min should be the same as the currently approved dose in adults with normal renal function.

- The text: "(to be divided into 2-3 daily doses)" should be omitted.]

For fixed dose combination products containing metformin:

Posology

[...]

Adults with normal renal function (GFR ≥ 90 mL/min)

[...]

Renal impairment

[...]

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis (see 4.4) should be reviewed before considering initiation of metformin in patients with GFR < 60 ml/min.

If no adequate strength of [product name] is available, individual monocomponents should be used instead of the fixed dose combination.

[...]

GFR ml/min	Metformin	[other monocomponent]
60-89	Maximum daily dose is 3000 mg Dose reduction may be considered in relation to declining renal function.	[relevant text]
45-59	Maximum daily dose is 2000 mg The starting dose is at most half of the maximum dose.	
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	
<30	Metformin is contraindicated	

[...]

For both products containing metformin as single agent and for fixed dose combination products containing metformin:

4.3 Contraindications

[This section should be revised as follows:]

[...]

- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Severe renal failure (GFR < 30 mL/min)

[...]

4.4 Special warnings and precautions for use

[Warnings should be revised as follows:]

[...]

Lactic acidosis

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

[...]

Administration of iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.5.

[...]

Renal function

GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2. Metformin is contraindicated in patients with GFR < 30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function, see section 4.3.

[...]

Surgery

Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

[...]

4.5 Interaction with other medicinal products and other forms of interaction

[The wording should be revised as follows:]

[...]

Concomitant use not recommended

[...]

Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

[...]

Iodinated contrast agents

Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.4.

[...]

Combinations requiring precautions for use

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

[...]

B. Package leaflet

[The following texts should be added to or replace existing texts, as appropriate:]

- **Section 2: What you need to know before you <take> <use> <Product name>**

- Do not <take> <use> <Product name>:

[...]

- If you have severely reduced kidney function.

[...]

- if you have uncontrolled diabetes, with, for example, severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see "Risk of lactic acidosis" below) or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell.

[...]

- Warnings and precautions

Risk of lactic acidosis

<Product name> may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease).

If any of the above apply to you, talk to your doctor for further instructions.

[...]

Stop taking <Product name> for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions.

[...]

Stop taking <Product name> and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma.

Symptoms of lactic acidosis include:

- vomiting
- stomach ache (abdominal pain)
- muscle cramps
- a general feeling of not being well with severe tiredness
- difficulty in breathing
- reduced body temperature and heartbeat

[...]

Lactic acidosis is a medical emergency and must be treated in a hospital.

[...]

If you need to have major surgery you must stop taking <Product name> during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with <Product name>.

[...]

During treatment with <Product name>, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.

- o Other medicines and <Product name>

If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example in the context of an X-ray or scan, you must stop taking <Product name> before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with <Product name>.

[...]

Tell your doctor if you are taking, have recently taken or might take any other medicines. You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dosage of <Product name>. It is especially important to mention the following:

[...]

- medicines which increase urine production (diuretics)
- medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as ibuprofen and celecoxib)
- certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists)

- o <Product name> with alcohol

Avoid excessive alcohol intake while taking <Product name> since this may increase the risk of lactic acidosis (see section "Warnings and precautions").

- **Section 3: How to <take> <use> <Product name>**

[...]

<If you have reduced kidney function, your doctor may prescribe a lower dose.> *[Text to be included for products where dose reduction is recommended, only if the PL provides specific information about the dose]*

[...]

- **Section 4: Possible side effects**

[Include among the most serious side effects at the top of section 4:]

[...]

<Product name> may cause a very rare (may affect up to 1 user in 10,000), but very serious side effect called lactic acidosis (see section "Warnings and precautions"). If this happens you must **stop taking <Product name> and contact a doctor or the nearest hospital immediately**, as lactic acidosis may lead to coma.

[...]