Version 4.0, 02/2016

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

/.../ 500 mg prolonged release tablets
/.../ 750 mg prolonged release tablets
/.../ 1000 mg prolonged release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release tablet contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base.
Each prolonged release tablet contains 750 mg metformin hydrochloride corresponding to 585 mg metformin base.
Each prolonged release tablet contains 1000 mg metformin hydrochloride corresponding to 780 mg metformin base.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged release tablet.

/…/ 500 mg prolonged release tablets are white to off-white, capsule shaped uncoated tablets, 16.50 mm in length, 8.20 mm in width and 6.70 mm in thickness, debossed with 'XR500' on one side and plain on other side.

/…/ 750 mg prolonged release tablets are white to off-white, capsule shaped, uncoated tablets, 19.60 mm in length, 9.30 mm in width and 7.40 mm in thickness, debossed with 'XR 750' on one side and plain on other side

/…/ 1000 mg prolonged release tablets are white to off-white, capsule shaped, uncoated tablets, 21.10 mm in length, 10.10 mm in width and 8.90 mm in thickness, debossed with 'XR 1000' on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. Metformin prolonged release tablets may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

4.2 Posology and method of administration

Posology

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

Monotherapy and combination with other oral anti-diabetic agents
The usual starting dose is one /.../ 500 mg prolonged release tablet once daily.

After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dose is 4 tablets of /.../ 500 mg daily.

Dosage increases should be made in increments of 500 mg every 10-15 days, up to a maximum of 2000 mg once daily with the evening meal. If glycaemic control is not achieved on 2000 mg once daily, 1000 mg twice daily should be considered, with both doses being given with food, at the time of the morning and evening meals. If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.

In patients already treated with metformin tablets, the starting dose of /.../ prolonged release tablets should be equivalent to the daily dose of metformin immediate release tablets. In patients treated with metformin at a dose above 2000 mg daily, switching to /.../ prolonged release tablets is not recommended.

/.../ 750 mg and 1000 mg prolonged release tablets are intended as maintenance therapy for patients currently treated with metformin tablets (prolonged or immediate release).

The dose of /.../ 750 mg or 1000 mg prolonged release tablets should be equivalent to the daily dose of metformin tablets (prolonged or immediate release), up to a maximum dose of 1500 mg or 2000 mg respectively, given with the evening meal. After 10 to 15 days, it is recommended to check that the dose of /…/ 750 mg or 1000 mg is adequate on the basis of blood glucose measurements.

In the event of transfer from another oral anti-diabetic agent: The other agent should be discontinued and titration should begin with /…/ 500 mg prolonged release tablets as indicated above, before switching to /…/ 750 mg or /…/ 1000 mg.

Combination with insulin
Metformin and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose of metformin is one 500 mg prolonged release tablet once daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

For patients already treated with metformin and insulin in combination therapy, the dose of /.../ 750 mg or 1000 mg prolonged release tablets should be equivalent to the daily dose of metformin tablets up to a maximum of 1500 mg or 2000 mg respectively, given with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements.

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	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.	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.

Elderly

Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary (see section 4.4).

Paediatric population
In the absence of available data, /.../ prolonged release tablets should not be used in children.

Method of administration
/.../ should be administered with food and swallowed whole with a glass of water. /.../ should be given with the evening meal when administered once daily. The tablets should not be chewed, split or crushed.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Severe renal failure (GFR <30 ml/min)
- Acute conditions with the potential to alter renal function such as:
  - dehydration,
  - severe infection,
  - shock,
- Acute or chronic disease which may cause tissue hypoxia such as:
  - cardiac or respiratory failure,
  - recent myocardial infarction,
  - shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism

4.4 Special warnings and precautions for use

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.

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.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID).

Administration of iodinated contrast agents
Intravascular administration of iodinated contrast agens 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.

Surgery
Metformin must be discontinued at the time of surgery under general, spinal or epidural anesthesia. 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.

Other precautions
All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.

The usual laboratory tests for diabetes monitoring should be performed regularly.

Metformin alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulphonylureas or meglitinides).

The tablet shells may be present in the faeces. It is recommended that patients be advised that this is normal.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Avoid consumption of alcohol or alcohol-containing medicinal products.

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.

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics). More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product.

4.6 Fertility, pregnancy and lactation

Pregnancy
Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality.

A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development (see section 5.3).

When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with metformin but insulin be used to maintain blood glucose levels as close to normal as possible to reduce the risk of malformations of the foetus.

Breastfeeding
Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding is not recommended during metformin treatment. A decision on whether to discontinue breast-feeding should be made, taking into account the benefit of breast-feeding and the potential risk to adverse effects on the child.

Fertility
Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

4.7 Effects on ability to drive and use machines

Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.

However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (e.g. sulphonylureas, insulin, or meglitinides).

4.8 Undesirable effects

In post marketing data and in controlled clinical studies, adverse event reporting in patients treated with metformin prolonged release tablets was similar in nature and severity to that reported in patients treated with metformin immediate release tablets.

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, which resolve spontaneously in most cases.

The following adverse reactions may occur under treatment with metformin.

Frequencies are defined as follows: very common: ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1,000 to <1/100; rare ≥1/10,000 to <1/1,000; very rare <1/10,000.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders
Very rare: Lactic acidosis (see section 4.4).

Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

Nervous system disorders
Common: Taste disturbance

Gastrointestinal disorders
Very common: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and

resolve spontaneously in most cases. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders
Very rare: Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders
Very rare: Skin reactions such as erythema, pruritus, urticaria.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes; blood glucose lowering drugs, excl. insulins, ATC code: A10BA02.

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Mechanism of action
Metformin may act via 3 mechanisms:

(1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis;
(2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation;
(3) and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

Pharmacodynamic effects
In clinical studies, the major non-glycaemic effect of metformin is either weight stability or modest weight loss.

In humans, independently of its action on glycaemia, immediate release metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: immediate release metformin reduces total cholesterol, LDL cholesterol and triglyceride levels. A similar action has not been demonstrated with the prolonged release formulation, possibly due to the evening administration, and an increase in triglycerides may occur.

Clinical efficacy and safety

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in overweight type 2 diabetic patients treated with immediate release metformin as first-line therapy after diet failure. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/ 1000 patient-years) versus diet alone (43.3 events/ 1000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/ 1000 patient-years), p=0.0034;
- a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/ 1000 patient-years, p=0.017;
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/ 1000 patient-years versus diet alone 20.6 events/ 1000 patient-years (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/ 1000 patient-years (p=0.021);
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/ 1000 patient-years, diet alone 18 events/ 1000 patient-years (p=0.01).

For metformin used as second-line therapy, in combination with a sulphonylurea, benefit regarding clinical outcome has not been shown.

In type 1 diabetes, the combination of metformin and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established.

5.2 Pharmacokinetic properties

Absorption

After an oral dose of the prolonged release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a T_{max} at 7 hours (T_{max} for the immediate release tablet is 2.5 hours).

At steady state, similar to the immediate release formulation, C_{max} and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000 mg of metformin prolonged release tablets is similar to that observed after administration of 1000 mg of metformin immediate release tablets b.i.d.

Intrasubject variability of C_{max} and AUC of metformin prolonged release is comparable to that observed with metformin immediate release tablets.

When the prolonged release tablet is administered in fasting conditions the AUC is decreased by 30% (both C_{max} and T_{max} are unaffected).

Mean metformin absorption from the prolonged release formulation is almost not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000 mg of metformin as prolonged release tablets.

Following a single oral administration in the fed state of one tablet of Metformin 1000 mg prolonged release tablets, a mean peak plasma concentration of 1214 ng/ml is achieved with a median time of 5 hours (range of 4 to 10 hours).

Metformin 1000 mg prolonged release tablets were shown to be bioequivalent to Metformin 500 mg prolonged release tablets at a 1000 mg dose with respect to C_{max} and AUC in healthy fed and fasted subjects.

When the 1000 mg prolonged release tablet is administered in fed conditions the AUC is increased by 77% (C_{max} is increased by 26% and T_{max} is slightly prolonged by about 1 hour).

Distribution
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Vd ranged between 63-276 L.

Biotransformation
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination
Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate
Silica, colloidal anhydrous
Povidone K30
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

14, 20, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 180, 600 tablets in blister strips composed of aluminium foil and PVC.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

<[To be completed nationally]>

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

/.../ 500 mg prolonged release tablets
/.../ 750 mg prolonged release tablets
/.../ 1000 mg prolonged release tablets

metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged release tablet contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base.
Each prolonged release tablet contains 750 mg metformin hydrochloride corresponding to 585 mg metformin base.
Each prolonged release tablet contains 1000 mg metformin hydrochloride corresponding to 780 mg metformin base.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 prolonged release tablets
20 prolonged release tablets
28 prolonged release tablets
30 prolonged release tablets
50 prolonged release tablets
56 prolonged release tablets
60 prolonged release tablets
84 prolonged release tablets
90 prolonged release tablets
100 prolonged release tablets
112 prolonged release tablets
120 prolonged release tablets
180 prolonged release tablets
600 prolonged release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.
Swallow the tablets whole with a glass of water. Do not chew, split or crush the tablets.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use with special attention for the information on lactic acidosis in section 2.

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

<[To be completed nationally]>

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

/.../ 500 mg prolonged release tablets
/.../ 750 mg prolonged release tablets
/.../ 1000 mg prolonged release tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

< PC: {number} [product code]
SN: {number} [serial number]
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

/.../ 500 mg prolonged release tablets
/.../ 750 mg prolonged release tablets
/.../ 1000 mg prolonged release tablets

metformin hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

{Name}

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

BN:

5. OTHER

PACKAGE LEAFLET

Package leaflet: Information for the user

/.../ 500 mg, 750 mg, 1000 mg prolonged release tablets

metformin hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor,or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What /.../ is and what it is used for

/.../ contains the active ingredient metformin hydrochloride and belong to a group of medicines called biguanides, used in the treatment of diabetes.

/.../ is used for the treatment of Type 2 (non-insulin dependent) diabetes mellitus in adults when diet and exercise changes alone have not been enough to control blood glucose (sugar). Insulin is a hormone that enables body tissues to take glucose from the blood and to use it for energy or for storage for future use. People with Type 2 diabetes do not make enough insulin in their pancreas or their body does not respond properly to the insulin it does make. This causes a build-up of glucose in the blood which can cause a number of serious long-term problems so it is important that you continue to take your medicine, even though you may not have any obvious symptoms. /.../ makes the body more sensitive to insulin and helps return to normal the way your body uses glucose.

/.../ is associated with either a stable body weight or modest weight loss.

/.../ is specially made to release the drug slowly in your body and therefore are different to many other types of tablet containing metformin.

2. What you need to know before you take /.../

Do not take /.../:
- If you are allergic to metformin or to any of the other ingredients of this medicine (listed in section 6).
- If you have long-term liver problems.
- 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.

- If you have a severe infection or have recently suffered a severe injury.
- If you have been treated for heart problems or have recently had a heart attack or have severe circulatory problems or breathing difficulties.
- If you are a heavy drinker of alcohol.

Warnings and precautions

After you have started taking your medicine:
If you have diabetes you should have your blood or urine tested for sugar regularly. During treatment with /…/ 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.

Risk of lactic acidosis
/…/ 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 /…/ 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 /…/ 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 /…/ during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with /…/.

You may see some remains of the tablets in your stools. Do not worry as this is normal for this type of tablet.

You should continue to follow any dietary advice that your doctor has given you and you should make sure that you eat carbohydrates regularly throughout the day.

Do not stop taking this medicine without speaking to your doctor

Children and adolescents
Children and adolescents should not use this medicine. It is not known if this medicine is safe and effective when used in children and adolescents under 18 years of age.

Other medicines and /.../
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 /…/ before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with /…/.

Tell your doctor or pharmacist 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 /…/. 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)
- Steroids such as prednisolone, mometasone, beclometasone.
- Sympathomimetic medicines including epinephrine and dopamine used to treat heart attacks and low blood pressure. Epinephrine is also included in some dental anaesthetics.

/.../ with food, drink and alcohol
You should take /.../ with or immediately after food e.g. with your evening meal.
Avoid excessive alcohol intake while taking /…/ since this may increase the risk of lactic acidosis (see section "Warnings and precautions").

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
It is recommended not to take this medicine if you are breast-feeding or if you are planning to breast-feed your baby.

Driving and using machines
/.../ taken on its own does not cause 'hypoglycemia' (symptoms of low blood sugar, such as faintness, confusion and increased sweating) and therefore should not affect your ability to drive or use machinery.
You should be aware, however, that /.../ taken with other antidiabetic medicines can cause low blood sugar, so in this case you should take extra care when driving or operating machinery.

3. How to take /.../

Your doctor may prescribe /.../ for you to take on its own, or in combination with other oral antidiabetic medicines or insulin.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dosage
Usually you will start treatment with 500 milligrams /.../ daily. After you have been taking /.../ for about 2 weeks, your doctor may measure your blood sugar and adjust the dose. The maximum daily dose is 2000 milligrams of /.../. If you have reduced kidney function, your doctor may prescribe a lower dose

How to take the tablets
Normally, you should take the tablets once a day, with your evening meal.
In some cases, your doctor may recommend that you take the tablets twice a day. Always take the tablets with food.
Swallow the tablets whole with a glass of water, do not chew, split or crush the tablets.

Use in children and adolescents
Children and adolescents below 18 years should not use this medicine.

Use in elderly
The dose will be determined after tests have been carried out on your kidney function.

If you take more /.../ than you should
If you take extra tablets by mistake you need not worry, but if you have unusual symptoms, contact your doctor. These symptoms may include weakness, confusion, fast breathing and new onset of nausea, vomiting or stomach pain. If the overdose is large, lactic acidosis is more likely and this is a medical emergency requiring treatment in hospital (see also under '4. Possible side effects').

If you forget to take /.../
Take it as soon as you remember with some food. Do not take a double dose to make up for a forgotten dose.

If you stop taking /.../
You should not stop taking this medicine without talking to your doctor first. If you stop taking /.../, your blood sugar may rise again.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you notice any of the following side effects, stop taking /.../ and see your doctor immediately:

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

Frequency not known (frequency cannot be estimated from the available data)
- Abnormal liver function tests and hepatitis (inflammation of the liver) which may result in jaundice. If you develop yellowing of the eyes and/or skin contact your doctor immediately.

Other possible side effects are listed by frequency as follows:

Very common (may affect more than 1 in 10 people):
- Diarrhoea, nausea, vomiting, stomach ache or loss of appetite. If you get these, do not stop taking the tablets as these symptoms will normally go away in about 2 weeks.

Common (may affect up to 1 in 10 people):
- Taste disturbance

Very rare (may affect up to 1 in 10,000 people):
- Decreased vitamin B_{12} levels which may result in anaemia
- Skin rashes including redness, itching and hives.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store /.../

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What /.../ contains

- The active substance is metformin (as hydrochloride). Each prolonged release tablet contains 500 mg, 750 mg or 1000 mg of metformin hydrochloride corresponding to 390 mg, 585 mg and 780 mg metformin base, respectively.
- The other ingredients are magnesium stearate, colloidal anhydrous silica, povidone K30 and hypromellose.

What /.../ looks like and contents of the pack

/.../ 500 mg prolonged release tablets are white to off-white, capsule shaped uncoated tablets, 16.50 mm in length, 8.20 mm in width and 6.70 mm in thickness, debossed with 'XR500' on one side and plain on other side.
/.../ 750 mg prolonged release tablets are white to off-white, capsule shaped, uncoated tablets, 19.60 mm in length, 9.30 mm in width and 7.40 mm in thickness, debossed with 'XR 750' on one side and plain on other side.
/.../ 1000 mg prolonged release tablets are white to off-white, capsule shaped, uncoated tablets, 21.10 mm in length, 10.10 mm in width and 8.90 mm in thickness, debossed with 'XR 1000' on one side and plain on other side.

/.../ is available in blister packs containing 14, 20, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 180, 600 tablets.

Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder

<[To be completed nationally]>

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

Manufacturer
Geryon Pharma Limited
18 Owen Drive
Liverpool
Merseyside
L24 1YA
United Kingdom

This medicinal product is authorised in the Member States of the EEA under the following names:

Denmark – LYOMET
Hungary – LYOMET XR 500,750,1000 mg Retard tabletta
Poland – LYOMET SR
Czech Republic – GLUCOMET
United Kingdom – Metformin 500 mg,750 mg,1000 mg Prolonged –release Tablets

Slovak Republic – LYOMET SR 500,750,1000mg

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>

<[To be completed nationally]>