Merck

Glucophage XR 500mg – 750mg – 1000mg
Extended Release Tablets

Metformin hydrochloride

1. NAME OF THE MEDICINAL PRODUCT
Glucophage XR 500 mg extended release tablet
Glucophage XR 750 mg extended release tablet
Glucophage XR 1000 mg extended release tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One Glucophage XR 500 mg extended release tablet contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base.
One Glucophage XR 750 mg extended release tablet contains 750 mg metformin hydrochloride corresponding to 585 mg metformin base.
One Glucophage XR 1000 mg extended release tablet contains 1000 mg metformin hydrochloride corresponding to 780 mg metformin base.
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Extended release tablet
Glucophage XR 500 mg: White to off-white, capsule-shaped, biconvex tablet, debossed on one side with “500”
Glucophage XR 750 mg: White to off-white, capsule-shaped, biconvex tablet, debossed on one side with '750' and on the other side with 'Merck'.
Glucophage XR 1000 mg: White to off-white, capsule-shaped, biconvex tablet, debossed on one side with “1000” and on the other side with 'Merck'.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications

- Reduction in the risk or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with IGT* and/or IFG* who are:
  - at high risk for developing overt type 2 diabetes mellitus (see section 5.1) and
  - not suitable for intensive lifestyle modifications.

Treatment with Glucophage XR must be based on a risk score incorporating appropriate measures of glycaemic control and including evidence of high cardiovascular risk (see section 5.1).

*IGT: Impaired Glucose Tolerance; IFG: Impaired Fasting Glucose

- 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.

Glucophage XR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

4.2 Posology and method of administration

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

Reduction in the risk or delay of the onset of type 2 diabetes
- Metformin should only be considered where intensive lifestyle modifications are not feasible.
- The therapy should be initiated with one tablet Glucophage XR 500 mg once daily with the evening meal.
- After 10 to 15 days dose adjustment on the basis of blood glucose measurements is recommended . A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dose is 2000 mg once daily with the evening meal.
- It is recommended to regularly monitor (every 3-6 months) the glycaemic status (OGTT and/or FPG and/or HbA1c value) as well as the risk factors to evaluate whether treatment needs to be continued, modified or discontinued.
- A decision to re-evaluate therapy is also required if the patient subsequently implements improvements to diet and/or exercise, or if changes to the medical condition will allow increased lifestyle interventions to be possible.

Monotherapy and combination with other oral antidiabetic agents in Type 2 diabetes mellitus.

Glucophage XR 500 mg
- The usual starting dose of Glucophage XR 500 mg is one tablet once daily with the evening meal.

- Glucophage XR tablets must be swallowed whole and never crushed or chewed.

- After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements.

- To improve gastrointestinal tolerability, dosage increase is recommended in increments of 500 mg every 10 to15 days, up to 2000 mg once daily with the evening meal. If glycaemic control is not achieved on Glucophage XR 2000 mg once daily, Glucophage XR 1000 mg twice daily should be considered, with both doses being given with food. 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 Glucophage XR 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 Glucophage XR is not recommended.

Glucophage XR 750 mg
- Glucophage XR 750 mg is intended for patients who are already treated with metformin tablets (extended or immediate release). The dose of Glucophage XR 750 mg should be equivalent to the daily dose of metformin tablets (extended or immediate release), up to a maximum dose of 1500 mg given with the evening meal.

- After 10 to 15 days dose adjustment on the basis of blood glucose measurements is recommended. A slow increase of dose may improve gastrointestinal tolerability. The recommended dose of Glucophage XR 750mg is 2 tablets once daily. If glycaemic control is not achieved on Glucophage XR 1500 mg once daily, the dose may be increased to a maximum dose of 2000 mg once daily. If glycaemic control is not achieved on Glucophage XR 2000 mg once daily, Glucophage XR 1000 mg twice daily should be considered, with both doses being given with food. If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.

Glucophage XR 1000 mg
- Glucophage XR 1000 mg is intended as a maintenance therapy for patients treated with either 1000 mg or 2000 mg of metformin hydrochloride. On switch, the daily dose of Glucophage XR should be equivalent to the current daily dose of metformin hydrochloride.

- Glucophage XR 1000 mg should be taken once daily with the evening meal at a maximum recommended dose of 2 tablets per day. If glycaemic control is not achieved on Glucophage XR 2000 mg once daily, Glucophage XR 1000 mg twice daily should be considered, with both doses being given with food. If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.

Combining Glucophage XR dosage strengths
The combined use of different strengths of Glucophage XR 500, Glucophage XR 750 or Glucophage XR 1000 is not recommended. Only one strength (Glucophage XR 500, Glucophage XR 750 or Glucophage XR 1000) should be used at a time in order to avoid accidentally exceeding the recommended upper daily dose limit of 2000mg.

Transfer from another oral antidiabetic agent
If transfer from another oral antidiabetic agent is intended, discontinue the other agent and initiate Glucophage XR 500 mg at the dose indicated above, before switching to Glucophage XR 750mg or Glucophage XR 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 Glucophage XR is 500mg once daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

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).

Benefit in the reduction of risk or delay of the onset of type 2 diabetes mellitus has not been established in patients 75 years and older (see section 5.1) and metformin initiation is therefore not recommended in these patients (see section 4.4).

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	Additional considerations
60-89	2000 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.

Paediatric population
In the absence of available data, Glucophage XR should not be used in children.

4.3 Contra-indications
- Hypersensitivity to metformin hydrochloride or to any of the excipients.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma.
- Severe renal failure (GFR < 30mL/min).
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, 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 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.

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function.
For patients with acute and unstable heart failure, metformin is contraindicated (see section 4.3).

Hepatic function

Because impaired hepatic function may significantly limit the ability to clear lactate and has been associated with some cases of lactic acidosis, Glucophage XR is contraindicated in patients with clinical and laboratory evidence of hepatic disease.

Hypoxic states

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause perenal azotemia. When such events occur in patients on Glucophage XR therapy, the drug should be promptly discontinued.

Hypoglycemia

Hypoglycemia does not occur in patients receiving Glucophage XR alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas, meglitinides and insulin) or ethanol.

Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Elderly:

Due to the limited therapeutic efficacy data in the reduction of risk or delay of type 2 diabetes in patients 75 years and older, metformin initiation is not recommended in these patients.

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.

Surgery:

Metformin must be discontinued 48 hours before elective surgery under general, spinal or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and only if normal renal function has been established.

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.
• It is recommended that vitamin B12 serum levels are monitored annually. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency (see section 4.8).
• The tablet shells may be present in the faeces. Patients should be advised that this is normal.

4.5 Interaction with other medicinal products and other forms of interactions

Concomitant use not recommended:
Alcohol:
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case 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.

Medicinal products with intrinsic hyperglycaemic activity (e.g glucocorticoids and tetracosactides (systemic and local routes), beta-2-agonists, danazol, chlorpromazine at high dosages of 100 mg per day and diuretics: 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 and upon discontinuation.

Organic cation transporters (OCT)
Metformin is a substrate of both transporters OCT1 and OCT2.
Co-administration of metformin with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

4.6 Pregnancy and lactation
Pregnancy
Uncontrolled hyperglycaemia in the periconceptional phase and during pregnancy is associated with increased risk of congenital abnormalities, pregnancy loss, pregnancy-induced hypertension, preeclampsia, and perinatal mortality. It is important to maintain blood glucose levels as close to normal as possible throughout pregnancy, to reduce the risk of adverse hyperglycaemia-related outcomes to the mother and her child.

Metformin crosses the placenta with levels that can be as high as maternal concentrations.

A large amount of data on pregnant women (more than 1000 exposed outcomes) from a register-based cohort study and published data (meta-analyses, clinical studies, and registries) indicates no increased risk of congenital abnormalities nor feto/ neonatal toxicity after exposure to metformin in the periconceptional phase and/or during pregnancy.

There is limited and inconclusive evidence on the metformin effect on the long-term weight outcome of children exposed in utero. Metformin does not appear to affect motor and social development up to 4 years of age in children exposed during pregnancy although data on long term outcomes are limited.

If clinically needed, the use of metformin can be considered during pregnancy and in the

periconceptional phase as an addition or an alternative to insulin.

Lactation
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 benefit of breast-feeding and the potential risk to adverse effect on the child.

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, meglitinides).

4.8 Undesirable effects
In post marketing data and in controlled clinical studies, adverse event reporting in patients treated with Glucophage XR was similar in nature and severity to that reported in patients treated with Glucophage immediate release.

The following adverse reactions may occur with metformin.
Frequencies are defined as follows: very common >1/10; common ≥1/100, <1/10; uncommon ≥1/1000, <1/100; rare ≥1/10,000, <1/1000; very rare <1/10,000.

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.

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

Metabolism and nutrition disorders:
Common: Vitamin B12 deficiency. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia (see section 4.4).
Very rare: Lactic acidosis (see section 4.4).

Hepatobiliary disorders:
Very rare: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

4.9 Overdose symptoms, emergency procedures, antidotes
Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. In a patient with lactic acidosis who is taking Glucophage XR, the drug should be discontinued immediately and general supportive measures promptly instituted. The most effective method to remove lactate and metformin is haemodialysis.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
ORAL ANTI-DIABETICS
(A10BA02: Gastrointestinal tract and metabolism)

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.

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).

In clinical studies use of metformin was associated with either a stable body weight 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 extended release formulation, possibly due to the evening administration, and an increase in triglycerides may occur.

Clinical efficacy:
Reduction in the risk or delay of type 2 diabetes mellitus
The **Diabetes Prevention Program** (DPP) was a multicenter randomised controlled clinical trial in adults assessing the efficacy of an intensive lifestyle intervention or metformin to prevent or delay the development of type 2 diabetes mellitus. Inclusion criteria were age ≥25 years, BMI ≥24 kg/m^2 (≥22 kg/m^2 for Asian-Americans), and impaired glucose tolerance plus a fasting plasma glucose of 95 – 125 mg/dl (or ≤125 mg/dl for American Indians). Patients were either treated with intensive lifestyle intervention, 2x850 mg metformin plus standard lifestyle change, or placebo plus standard lifestyle change.

The mean baseline values of the DPP participants (n=3,234 for 2.8 years) were age 50.6±10.7 years, 106.5±8.3 mg/dl fasted plasma glucose, 164.6±17.0 mg/dl plasma glucose two hours after an oral glucose load, and 34.0±6.7 kg/m^2 BMI.

Intensive lifestyle intervention as well as metformin significantly reduced the risk of developing overt diabetes compared to placebo, 58% (95% CI 48-66%) and 31% (95% CI 17-43%), respectively.

The advantage of the lifestyle intervention over metformin was greater in older persons.

The patients who benefited most from the metformin treatment were aged below 45 years, with a BMI equal or above 35kg/m^2, a baseline glucose 2 h value of 9.6-11.0 mmol/l, a baseline HbA1c equal or above 6.0% or with a history of gestational diabetes.

Table: Incidence of conversion to overt diabetes in DPP (DPP, 2002)

Variable	N° patients (%)	Incidence (cases/100 person years		Incidence reduction % (95%CI)
		Placebo	Metformin	
Overall	3234	11	7.8	31 (17 – 43)
Age (years)				
25-44	1000 (31)	11.6	6.7	44 (21 – 60)
45-59	1586 (49)	10.8	7.6	31 (10 – 46)
≥60	648 (20)	10.8	9.6	11 (-33 – 41)
Gender				
Male	1043 (32)	12.5	8.1	37 (14 – 54)
Female	2191 (68)	10.3	7.6	28 (10 – 43)
Race				
White	1768 (55)	10.3	7.8	24 (3 – 41)
African American	645 (20)	12.4	7.1	44 (16 – 63)
Hispanic	508 (16)	11.7	8.4	31 (-9 – 56)
American Indian	171 (5)	12.9	9.7	25 (-72 – 68)
Asian	142 (4)	12.1	7.5	38 (-55 – 75)
BMI (kg/m^2)				
22 - <30	1045 (32)	9.0	8.8	3 (-36 – 30)
30 - <35	995 (31)	8.9	7.6	16 (-19 – 41)
≥35	1194 (37)	14.3	7.0	53 (36 – 65)
FPG (mg/dl)				
95-109	2174 (67)	6.4	5.5	15 (-12 – 36)
110 - 125	1060 (33)	22.3	12.3	48 (33 – 60)
OGTT (mg/dl)				
140 – 153	1049 (32)	7.1	4.3	41 (11 – 61)
154 - 172	1103 (34)	10.3	6.6	38 (13 – 56)
173 - 199	1082 (34)	16.1	12.3	26 (3 – 43)

To prevent one case of overt diabetes during the three years in the whole population of the DPP, 6.9 patients had to participate in the intensive lifestyle group and 13.9 in the metformin group. The point of reaching a cumulative incidence of diabetes equal to 50% was delayed by about three years in the metformin group compared to placebo.

The **Diabetes Prevention Program Outcomes Study** (DPPOS) is the long-term follow-up study of the DPP including more than 87% of the original DPP population for long-term follow up.

Among the DPPOS participants (n=2776), the cumulative incidence of diabetes at year 15 is 62% in the placebo group, 56% in the metformin group, and 55% in the intensive lifestyle intervention group. Crude rates of diabetes are 7.0, 5.7 and 5.2 cases per 100 person-years among the placebo, metformin, and intensive lifestyle participants, respectively. Reductions in the diabetes risk were of 18% (hazard ratio (HR) 0.82, 95% CI 0.72–0.93; p=0.001) for the metformin group and 27% (HR 0.73, 95% CI 0.65–0.83; p<0.0001) for the intensive lifestyle intervention group, when compared with the placebo group. For an aggregate microvascular endpoint of nephropathy, retinopathy and neuropathy, the outcome was not significantly different between the treatment groups, but among the participants who had not developed diabetes during DPP/DPPOS, the prevalence of the aggregate microvascular outcome was 28% lower compared with those who had developed diabetes (Risk Ratio 0.72, 95% CI 0.63–0.83; p<0.0001). No prospective comparative data for metformin on macrovascular outcomes in patients with IGT and/or IFG are available.

Published risk factors for type 2 diabetes include: Asian or black ethnic background, age above 40, dyslipidaemia, hypertension, obesity or being overweight, age, 1st degree family history of diabetes, history of gestational diabetes mellitus, and polycystic ovary syndrome (PCOS).

Consideration must be given to current national guidance on the definition of prediabetes.

Patients at high risk should be identified by a validated risk-assessment tool.

Treatment of type 2 diabetes mellitus
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 Glucophage XR 500 mg, metformin absorption is significantly delayed compared to the immediate-release tablet (Tmax at 2.5 hours) with a Tmax at 7 hours.

Following a single oral administration of 1500 mg of Glucophage XR 750 mg, a mean peak plasma concentration of 1193 ng/mL is achieved with a median value of 5 hours and a range of 4 to 12 hours. Glucophage XR 750 mg was shown to be bioequivalent to Glucophage XR 500 mg at a 1500 mg dose with respect to Cmax and AUC in healthy fed and fasted subjects.

Following a single oral administration in the fed state of one tablet of Glucophage XR 1000 mg, a mean peak plasma concentration of 1214 ng/mL is achieved with a median time of 5 hours (range of 4 to 10 hours). Glucophage XR 1000 mg was shown to be bioequivalent to Glucophage XR 500 mg at a 1000 mg dose with respect to Cmax and AUC in healthy fed and fasted subjects.

At steady state, similar to the immediate-release formulation, Cmax and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000 mg metformin prolonged-release is similar to that observed after administration of 1000 mg metformin immediate-release twice daily.

Intrasubject variability of Cmax and AUC of metformin prolonged-release is comparable to that observed with metformin immediate-release.

When 2 tablets of 500 mg metformin prolonged-release is administered in fed conditions the AUC is increased by approximately 70% (both Cmax and Tmax are only slightly increased.

When the 1000 mg prolonged release tablet are administered in fed conditions the AUC is increased by 77% (Cmax is increased by 26 % and Tmax is slightly prolonged by about 1 hour).

Metformin absorption from the prolonged-release formulation is not altered by meal composition.

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

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 volume of distribution (Vd) ranged between 63-276 L.

Metabolism:
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
Preclinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity reproduction.

6. PHARMACEUTICAL PARTICULARS
6.1 List of Excipients
Glucophage XR 500 mg: Magnesium stearate, sodium carboxymethylcellulose, hypromellose, microcrystalline cellulose.

Glucophage XR 750 mg & 1000mg: Magnesium stearate, sodium carboxymethylcellulose, hypromellose.

6.2 Incompatibilities
None

6.3 Shelf life
36 months

6.4 Presentation
Glucophage XR 500 mg & 750mg: 15 tablets per blister, pack size of 2 or 4 blister strips.

Glucophage XR 1000 mg: 10 tablets per blister, pack size of 3 or 6 blister strips.

Not all presentations may be marketed locally

7. Product Owner
Merck Santé S.A.S,
37, rue St Romain
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8. Date of revision of the text
June 2022 (Based on CCDS V8.0 & 9.0)