SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

GLUCOPHAGE 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

[to be completed nationally: imprinting (if applicable) and dimensions of the tablet]
White, circular, convex film-coated tablets *[e.g. 12 mm]* in diameter and *[e.g. 5 mm]* high *[engraved GL 500]*.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.
  — In adults, Glucophage may be used as monotherapy or in combination with other oral antidiabetic agents or with insulin.
  — In children from 10 years of age and adolescents, Glucophage may be used as monotherapy or in combination with insulin.

  A reduction of diabetic complications has been shown in overweight type 2 diabetic adult patients treated with metformin as first-line therapy after diet failure (see section 5.1).

- Reduction in the risk or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with IGT* and/or IFG*, and/or increased HbA1C* who are:
  — at high risk for developing overt type 2 diabetes mellitus (see section 5.1) and
  — still progressing towards type 2 diabetes mellitus despite implementation of intensive lifestyle change for 3 to 6 months.

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

  Lifestyle modifications should be continued when metformin is initiated, unless the patient is unable to do so because of medical reasons.

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

4.2 Posology and method of administration

<u>*Posology*</u>

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

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

The usual starting dose is 500 mg or 850 mg metformin hydrochloride 2 or 3 times daily given during or after meals.
After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability.
The maximum recommended dose of metformin hydrochloride is 3 g daily, taken as 3 divided doses.
If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate metformin at the dose indicated above.

Monotherapy in reduction in the risk or delay of the onset of type 2 diabetes mellitus:

- Metformin should only be considered where lifestyle modifications for 3 to 6 months have not resulted in adequate glycemic control.
- The therapy should be initiated with 500 mg or 850 mg metformin hydrochloride once daily given during or after a meal.
- After 10 to 15 days dose adjustment on the basis of blood glucose measurements is recommended (OGTT and/or FPG and/or HbA1c values to be within the normal range). A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended daily dose is 3000 mg of metformin hydrochloride, taken as 3 divided doses.
- It is recommended to regularly monitor (every 3-6 months) the glycemic 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.

Combination with insulin

Metformin and insulin may be used in combination therapy to achieve better blood glucose control. Metformin hydrochloride is given at the usual starting dose of 500 mg or 850 mg 2 or 3 times 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) d 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 (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.

Paediatric population

Monotherapy in type 2 diabetes mellitus and combination with insulin

— Glucophage can be used in children from 10 years of age and adolescents.
— The usual starting dose is 500 mg or 850 mg metformin hydrochloride once daily, given during or after meals.

After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of metformin hydrochloride is 2 g daily, taken as 2 or 3 divided doses.

4.3 Contraindications

— Hypersensitivity to metformin or to any of the excipients listed in section 6.1.
— Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
— Diabetic pre-coma.
— Severe renal failure (GFR < 30 mL/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 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.

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).

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 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.

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.

Paediatric population

The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is initiated.

No effect of metformin on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially prepubescent children, is recommended.

Children aged between 10 and 12 years

Only 15 subjects aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents. Although efficacy and safety of metformin in these children did not differ from efficacy and safety in older children and adolescents, particular caution is recommended when prescribing to children aged between 10 and 12 years.

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. sulfonylureas or meglitinides).

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.

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 and upon its 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, trimethoprime, 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 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 impaired glycemic control and diabetes are 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.

Breast-feeding

Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breast-feeding 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. sulfonylureas, insulin or meglitinides).

4.8 Undesirable effects

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take metformin in 2 or 3 daily doses and to increase slowly the doses.

The following adverse reactions may occur under treatment with metformin. Frequencies are defined as follows: very common: ≥1/10; common ≥1/100, <1/10; uncommon ≥1/1,000, <1/100; rare ≥1/10,000, <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. To prevent them, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. 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

Paediatric population

In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

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: Blood glucose lowering drugs. Biguanides; ATC code: A10BA02

Mechanism of action

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:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
- 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 (GLUTs) known to date.

Pharmacodynamic effects

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, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical efficacy

Type 2 diabetes mellitus
The prospective randomised study (UKPDS) has established the long-term benefit of intensive blood glucose control in adult patients with type 2 diabetes.

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 sulfonylurea 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 sulfonylurea 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).

Benefit regarding clinical outcome has not been shown for metformin used as second-line therapy, in combination with a sulfonylurea.
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.

Reduction in the risk or delay of the onset of type 2 diabetes mellitus
The **Diabetes Prevention Program** (DPP) was a multicenter randomized 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.

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 and/or increased HbA1C are available.

Published risk factors for type 2 diabetes include: Asian or black ethnic background, age above 40, dyslipidemia, 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 using accepted tools for diabetes risk assessment.

Paediatric population

Controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year demonstrated a similar response in glycaemic control to that seen in adults.

5.2 Pharmacokinetic properties

Absorption

After an oral dose of metformin hydrochloride tablet, maximum plasma concentration (C_{max}) is reached in approximately 2.5 hours (t_{max}). Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.
At the recommended metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 5 microgram/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following oral administration of a 850 mg tablet, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these findings is unknown.

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.

Characteristics in specific groups of patients

Renal impairment

The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations (see section 4.2).

Paediatric population

Single dose study: After single doses of metformin hydrochloride 500 mg paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (C_{max}) and systemic exposure (AUC0-t) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

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 and reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Povidone K 30
Magnesium stearate

Film-coating
Hypromellose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

1 (x100), 9, 20, 21, 30, 40, 50, 56, 60, 84, 90, 100, 120, 200, 500, 600 or 1000 tablets in blister packs (PVC-aluminium)
21, 30, 40, 50, 60, 100, 120, 300, 400, 500, 600 or 1000 tablets in plastic bottles (high-density polyethylene) with child-resistant caps (polypropylene).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF THE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

GLUCOPHAGE 500 mg film-coated tablets
metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

9 film-coated tablets
20 film-coated tablets
21 film-coated tablets
30 film-coated tablets
40 film-coated tablets
50 film-coated tablets
56 film-coated tablets
60 film-coated tablets
84 film-coated tablets
90 film-coated tablets
100 film-coated tablets
120 film-coated tablets
200 film-coated tablets
500 film-coated tablets
600 film-coated tablets
1000 film-coated tablets
1 (x100) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

8. EXPIRY DATE

EXP

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]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GLUCOPHAGE 500 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF THE BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

GLUCOPHAGE 500 mg film-coated tablets
metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

21 film-coated tablets
30 film-coated tablets
40 film-coated tablets
50 film-coated tablets
60 film-coated tablets
100 film-coated tablets
120 film-coated tablets
300 film-coated tablets
400 film-coated tablets
500 film-coated tablets
600 film-coated tablets
1000 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use..

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

8. EXPIRY DATE

EXP

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]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GLUCOPHAGE 500 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

GLUCOPHAGE 500 mg film-coated tablets
metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

21 film-coated tablets
30 film-coated tablets
40 film-coated tablets
50 film-coated tablets
60 film-coated tablets
100 film-coated tablets
120 film-coated tablets
300 film-coated tablets
400 film-coated tablets
500 film-coated tablets
600 film-coated tablets
1000 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

8. EXPIRY DATE

EXP

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]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GLUCOPHAGE 500 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

GLUCOPHAGE 500 mg film-coated tablets
metformin hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PACKAGE LEAFLET

Package leaflet: Information for the user

GLUCOPHAGE 500 mg film-coated 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. Do not pass it on to others. It may harm them, even if their symptoms 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 Glucophage is and what it is used for

Glucophage contains metformin**,** a medicine to treat diabetes. It belongs to a group of medicines called biguanides.

Insulin is a hormone produced by the pancreasthat makes your body take in glucose (sugar) from the blood. Your body uses glucose to produce energy or stores it for future use.
If you have diabetes, your pancreas does not make enough insulin or your body is not able to use properly the insulin it produces. This leads to a high level of glucose in your blood. Glucophage helps to lower your blood glucose to as normal a level as possible.

If you are an overweight adult, taking Glucophage over a long period of time also helps to lower the risk of complications associated with diabetes. Glucophage is associated with either a stable body weight or modest weight loss.

Glucophage is used to treat patients with type 2 diabetes (also called 'non-insulin dependent diabetes') when diet and exercise alone have not been enough to control your blood glucose levels. It is used particularly in overweight patients.

Adults can take Glucophage on its own or together with other medicines to treat diabetes (medicines taken by mouth or insulin).
Children 10 years and over and adolescents can take Glucophage on its own or together with insulin.

Glucophage is also used together with diet and exercise to lower the risk of developing Type 2 diabetes in overweight adults, when diet and exercise alone for 3 to 6 months have not been enough to control blood glucose (sugar). You are at high risk of developing Type 2 diabetes if you have additional conditions like high blood pressure, age above 40 years, an abnormal amount of lipids (fat) in the blood or a history of diabetes during pregnancy. **THE MEDICINE IS PARTICULARLY EFFECTIVE IF YOU ARE AGED BELOW 45 YEARS, ARE VERY OVERWEIGHT, HAVE HIGH BLOOD GLUCOSE LEVELS AFTER A MEAL OR DEVELOPED DIABETES DURING PREGNANCY.**

2. What you need to know before you take Glucophage

Do not take Glucophage
- if you are allergic (hypersensitive) to metformin or any of the other ingredients of this medicine (see 'What Glucophage contains' in section 6)
- if you have 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 lost too much water from your body (dehydration), such as due to long-lasting or severe diarrhoea, or if you have vomited several times in a row. Dehydration may lead to kidney problems, which can put you at risk for lactic acidosis (see 'Warnings and precautions').
- if you have a severe infection, such as an infection affecting your lung or bronchial system or your kidney. Severe infections may lead to kidney problems, which can put you at risk for lactic acidosis (see 'Warnings and precautions').
- if you are treated for acute heart failure or have recently had a heart attack, have severe problems with your circulation (such as shock) or have breathing difficulties. This may lead to a lack in oxygen supply to tissue which can put you at risk for lactic acidosis (see 'Warnings and precautions').
- if you drink a lot of alcohol

If any of the above applies to you, talk to your doctor, before you start taking this medicine.

Make sure you ask your doctor for advice, if:
- you need to have an examination such as X-ray or scan involving the injection of contrast medicines that contain iodine into your bloodstream
- you need to have major surgery

You must stop taking Glucophage for a certain period of time before and after the examination or the surgery. Your doctor will decide whether you need any other treatment for this time. It is important that you follow your doctor's instructions precisely.

Warnings and precautions

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

Glucophage on its own does not cause hypoglycaemia (a blood glucose level which is too low). However, if you take Glucophage together with other medicines to treat diabetes that can cause hypoglycaemia (such as sulphonylureas, insulin, meglitinides), there is a risk of hypoglycaemia. If you experience symptoms of hypoglycaemia such as weakness, dizziness, increased sweating, fast heart beating, visions disorders or difficulty in concentration, it usually helps to eat or drink something containing sugar.

During treatment with Glucophage, 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.

If you are older than 75 years, treatment with Glucophage should not be started to lower the risk of developing type 2 diabetes.

Other medicines and Glucophage

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

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 Glucophage. 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).
— beta-2 agonists such as salbutamol or terbutaline (used to treat asthma).
— corticosteroids (used to treat a variety of conditions, such as severe inflammation of the skin or in asthma).
— medicines that may change the amount of Glucophage in your blood, especially if you have reduced kidney function (such as verapamil, rifampicin; cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole, crizotinib, olaparib).
— other medicines used to treat diabetes.

Glucophage with alcohol

Avoid excessive alcohol intake while taking Glucophage since this may increase the risk of lactic acidosis (see section ‘Warnings and precautions’).

Pregnancy and breast-feeding

During pregnancy, you need insulin to treat your diabetes. Tell your doctor if you are, you think you might be or are planning to become pregnant, so that he or she may change your treatment.
This medicine is not recommended if you are breast-feeding or if you are planning to breast-feed your baby.

Driving and using machines

Glucophage on its own does not cause hypoglycaemia (a blood glucose level which is too low). This means that it will not affect your ability to drive or use machines.

However, take special care if you take Glucophage together with other medicines to treat diabetes that can cause hypoglycaemia (such as sulphonylureas, insulin, meglitinides). Symptoms of hypoglycaemia include weakness, dizziness, increased sweating, fast heart beat, vision disorders or difficulty in concentration. Do not drive or use machines if you start to feel these symptoms.

3. How to take Glucophage

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

Glucophage cannot replace the benefits of a healthy lifestyle. Continue to follow any advice about diet that your doctor has given you and get some regular exercise.

Recommended dose

Children 10 years and over and adolescents usually start with 500 mg or 850 mg Glucophage once a day. The maximum daily dose is 2000 mg taken as 2 or 3 divided doses. Treatment of children between 10 and 12 years of age is only recommended on specific advice from your doctor, as experience in this age group is limited.

Adults usually start with 500 mg or 850 mg Glucophage once to three times a day. The maximum daily dose is 3000 mg taken as 3 divided doses.

If you have reduced kidney function, your doctor may prescribe a lower dose.

If you take insulin too, your doctor will tell you how to start Glucophage.

Monitoring

— Your doctor will perform regular blood glucose tests and will adapt your dose of Glucophage to your blood glucose levels. Make sure that you talk to your doctor regularly. This is particularly important for children and adolescents or if you are an older person.
— Your doctor will also check at least once a year how well your kidneys work. You may need more frequent checks if you are an older person or if your kidneys are not working normally.

How to take Glucophage

Take Glucophage with or after a meal. This will avoid you having side effects affecting your digestion.

Do not crush or chew the tablets. Swallow each tablet with a glass of water.
— If you take one dose a day, take it in the morning (breakfast)

— If you take two divided doses a day, take them in the morning (breakfast) and evening (dinner)
— If you take three divided doses a day, take them in the morning (breakfast), at noon (lunch) and in the evening (dinner)

If, after some time, you think that the effect of Glucophage is too strong or too weak, talk to your doctor or pharmacist.

If you take more Glucophage than you should
If you have taken more Glucophage that you should have, you may experience lactic acidosis. Symptoms of lactic acidosis are non-specific such as vomitting, bellyache (abdominal pain) with muscle cramps, a general feeling of not being well with severe tiredness, and difficulty in breathing. Further symptoms are reduced body temperature and heart beat. **If you experience some of these symptoms, you should seek immediately medical attention, as lactic acidosis may lead to coma. Stop taking Glucophage immediately and contact a doctor or the nearest hospital straight away**.

If you forget to take Glucophage
Do not take a double dose to make up for a forgotten dose. Take the next dose at the usual time.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Glucophage can cause side effects, although not everybody gets them. The following side effects may occur:

Glucophage 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 Glucophage and contact a doctor or the nearest hospital immediately**, as lactic acidosis may lead to coma.

Very common side effects (in more than 1 in 10 people)
— digestive problems, such as feeling sick (nausea), being sick (vomiting), diarrhoea, bellyache (abdominal pain) and loss of appetite. These side effects most often happen at the beginning of the treatment with Glucophage. It helps if you spread the doses over the day and if you take Glucophage with or straight after a meal. **If symptoms continue, stop taking Glucophage and talk to your doctor**.

Common side effects (in less than 1 in 10 people)
— changes in taste.

Very rare side effects (**in less than 1 in 10,000 people**)
— lactic acidosis. This is a very rare but serious complication particularly if your kidneys are not working properly.
Symptoms of lactic acidosis are non-specific (see section 'Warning and precautions')
— abnormalities in liver function tests or hepatitis (inflammation of the liver; this may cause tiredness, loss of appetite, weight loss, with or without yellowing of the skin or whites of the eyes). If this happens to you, **stop taking Glucophage and talk to your doctor.**
— skin reactions such as redness of the skin (erythema), itching or an itchy rash (hives).
— low vitamin B12 levels in the blood.

Children and adolescents
Limited data in children and adolescents showed that adverse events were similar in nature and severity to those reported in adults.

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 Glucophage

Keep out of the sight and reach of children. If a child is treated with Glucophage, parents and caregivers are advised to oversee how this medicine is used.

This medicinal product does not require any special storage conditions.

Do not use Glucophage after the expiry date which is stated on the carton or the bottle or the blister after 'EXP'. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Glucophage contains

— The active substance is metformin hydrochloride. One film-coated tablet of Glucophage 500 mg contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base.
— The other ingredients are povidone K 30, magnesium stearate, hypromellose.

What Glucophage looks like and contents of the pack

[to be completed nationally: imprinting (if applicable) and dimensions of the tablet]
Glucophage 500 mg film-coated tablets are white, circular *[e.g.12 mm]* in diameter and *[e.g. 5 mm]* high, convex *[engraved GL 500]*.
The tablets are supplied in blister packs of 1 (x100), 9, 20, 21, 30, 40, 50, 56, 60, 84, 90, 100, 120, 200, 500, 600 or 1000 tablets and in plastic bottles with child-resistant caps of 21, 30, 40, 50, 60, 100, 120, 300, 400, 500, 600 or 1000 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
[to be completed nationally]

Manufacturer

Merck Santé s.a.s.
2 rue du Pressoir Vert
45400 Semoy
France

or

Merck KGaA
Frankfurter Str. 250
64293 Darmstadt
Germany

or (for Belgium and Luxembourg only)

Tjoapack Netherlands B.V.
Nieuwe Donk 9
Etten-Leur, 4879 AC

The Netherlands

or

Merck KGaA & Co. Werk Spittal
Hösslgasse 20
9800 Spittal/Drau
Austria

or

Merck S.L.
Poligono Merck
Mollet Del Vallès 08100 Barcelona
Spain

or

Famar Lyon
29 avenue Charles de Gaulle
69230 Saint-Genis Laval
France

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

Glucophage: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Latvia, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Sweden, United Kingdom

Merckformin: Hungary

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]