SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

GLUCOPHAGE 850 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 850 mg metformin hydrochloride corresponding to 662.9 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. 13.5 mm]* in diameter and *[e.g. 6.6 mm]* high *[engraved GL 850].*

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).

4.2 Posology and method of administration

Posology

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

Monotherapy 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.

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).

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 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.

Patients with known or suspected mitochondrial diseases:

In patients with known mitochondrial diseases such as Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome and Maternal inherited diabetes and deafness (MIDD), metformin is not recommended due to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease.

In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.

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.

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 may reduce vitamin B12 serum levels. 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. In case of suspicion of vitamin B12 deficiency (such as anemia or neuropathy), vitamin B12 serum levels

should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

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.
- 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 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.

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:

Common:
- Vitamin B12 decrease/deficiency (see section 4.4).

Very rare
- Lactic acidosis (see section 4.4).

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, on both basal and postprandial hyperglycaemia. It does not stimulate insulin secretion and therefore does not cause hypoglycaemia. Metformin reduces basal hyperinsulinemia, and in combination with insulin, reduces insulin requirement.

Metformin exerts its antihyperglycaemic effect via multiple mechanisms: Metformin reduces hepatic glucose production.
Metformin facilitates peripheral glucose uptake and utilization, in part by increasing insulin action.
Metformin alters glucose turnover in the gut: Uptake from circulation is increased and absorption from food is decreased. Additional mechanisms attributed to the gut include an increase in release of glucagon-like peptide 1 (GLP-1) and a decrease of bile acid resorption. Metformin alters the gut microbiome.

Metformin can improve the lipid profile in hyperlipidaemic individuals.

In clinical studies, use of metformin was associated with either a stable body weight or modest weight loss.

Metformin is an adenosine monophosphate-protein-kinase (AMPK) activator and increases the transport capacity of all types of membrane glucose transporters (GLUTs).

Clinical efficacy

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.

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), 8, 9, 10, 14, 20, 21, 30, 40, 50, 56, 60, 84, 90, 100, 120, 300, 600 or 1000 tablets in blister packs (PVC-aluminium)
30, 60, 200, 300 or 600 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

Merck (Pty) Ltd
1 Friesland Drive, Longmeadow Business Estate South, Modderfontein, 1645, South Africa

8. MARKETING AUTHORISATION NUMBER(S)

2928

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/11/2025

10. DATE OF REVISION OF THE TEXT

11/11/2025

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF THE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

GLUCOPHAGE 850 mg film-coated tablets metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 850 mg metformin hydrochloride corresponding to 662.9 mg metformin base.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

8 film-coated tablets
9 film-coated tablets
10 film-coated tablets
14 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
300 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

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GLUCOPHAGE 850 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 850 mg film-coated tablets metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 850 mg metformin hydrochloride corresponding to 662.9 mg metformin base.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
60 film-coated tablets
200 film-coated tablets
300 film-coated tablets
600 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

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GLUCOPHAGE 850 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 850 mg film-coated tablets metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 850 mg metformin hydrochloride corresponding to 662.9 mg metformin base.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
60 film-coated tablets
200 film-coated tablets
300 film-coated tablets
600 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

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GLUCOPHAGE 850 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

GLUCOPHAGE 850 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 850 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 pancreas that 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.

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 (listed 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 <u>Risk of</u>

<u>lactic acidosis</u>

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. Talk to your doctor promptly for further

instructions if:

- you are known to suffer from a genetically inherited disease affecting mitochondria (the

energy-producing components within cells) such as MELAS syndrome (Mitochondrial

Encephalopathy, myopathy, Lactic acidosis and Stroke-like episodes) or Maternal inherited diabetes and deafness (MIDD).
- you have any of these symptoms after starting metformin: seizure, declined cognitive abilities, difficulty with body movements, symptoms indicating nerve damage (e.g. pain or numbness), migraine and deafness.

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.

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

If you are pregnant, think you may be pregnant or are planning to have a baby, speak to your doctor in case any changes will be needed to your treatment or monitoring of your blood glucose levels.

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 this medicine 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 two or 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 vomiting, 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

medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine 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 (may affect 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 (may affect up to 1 in 10 people)
- changes in taste.
- decreased or low vitamin B12 levels in the blood (symptoms may include extreme tiredness (fatigue), a sore and red tongue (glossitis), pins and needles (paraesthesia) or pale or yellow skin). Your doctor may arrange some tests to find out the cause of your symptoms because some of these may also be caused by diabetes or due to other unrelated health problems.

Very rare side effects (**may affect up to 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).

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 this medicine 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 this medicine 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.

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 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 850 mg contains 850 mg metformin hydrochloride corresponding to 662.9 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 850 mg film-coated tablets are white, circular [*e.g. 13.5 mm]* in diameter and *[e.g. 6.6 mm]* high,convex *[engraved GL 850]*.
The tablets are supplied in blister packs of 1 (x100), 8, 9, 10, 14, 20, 21, 30, 40, 50, 56, 60, 84, 90,
100, 120, 300, 600 or 1000 tablets and in plastic bottles with child-resistant caps of 30, 60, 200, 300 or
600 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
Fran

ce or

Merck Healthcare KGaA Frankfurter Str.
250 64293 Darmstadt
German

y or

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

or (for Greece only)

Petsiavas S.A.
Agion Anargyron 21,
Kaliftaki, Kato Kifissia,
Attiki 145 64 Greece

This medicine is authorised in the Member States of the European Economic Area and United Kingdom (Northern Ireland) under the following names:

Spain: Dianben

Austria, Belgium, Bulgaria, Cyprus, Czech Republic, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Norway, Poland, Romania, Slovakia, Slovenia, Sweden, United Kingdom (Northern Ireland): Glucophage

Hungary: Merckformin

Portugal: Risidon

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

[To be completed nationally]