Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Metformin Mylan 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White, round, normal convex, film-coated tablets plain on both sides. Diameter about 12.0 mm.

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, Metformin Mylan film-coated tablets may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin.

• In children from 10 years of age and adolescents, Metformin Mylan film-coated tablets 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 one tablet of 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.

In patients receiving a high metformin dose (2 to 3 grams per day), it is possible to replace two Metformin Mylan 500 mg film-coated tablets with one Metformin Mylan 1000 mg film-coated tablet.

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 hydrochloride at the dose indicated above.

Combination with insulin:
Metformin hydrochloride and insulin may be used in combination therapy to achieve better blood glucose control.

Metformin hydrochloride is given at the usual starting dose of one tablet of 500 mg or 850 mg metformin, 2 or 3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

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

GFR mL/min	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.

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

Paediatric population:
Monotherapy and combination with insulin
• Metformin Mylan film-coated tablets can be used in children from 10 years of age and adolescents.
• The usual starting dose is one tablet of 500 mg or 850 mg metformin 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 is 2 g daily, taken as 2 or 3 divided doses.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
• Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
• 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.
• Acute or chronic disease which may cause tissue hypoxia such as:
  - cardiac or respiratory failure
  - recent myocardial infarction
  - shock.
• Hepatic insufficiency, acute alcohol intoxication, alcoholism.

4.4 Special warnings and precautions for use

Lactic acidosis:
Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal functioning 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 (> 5mmol/L) and an increased anion gap and lactate/pyruvate ratio.

. If metabolic acidosis is suspected, metformin hydrochloride should be discontinued and the patient should be hospitalised immediately (see section 4.9).

Renal function:
GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2. Metformin is contraindicated in patients with GFR < 30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function, see section 4.3.
Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID).

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 media
Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin hydrochloride 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 hydrochloride 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.

Children and adolescents:
The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin hydrochloride is initiated.

No effect of metformin hydrochloride 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 hydrochloride on these parameters in metformin-treated children, especially pre-pubescent 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 hydrochloride 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 hydrochloride 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).

Physicians should alert the patients on the risk and on the symptoms of lactic acidosis.

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 case of:
fasting, malnutrition or hepatic impairment.
Avoid consumption of alcohol and alcohol-containing medicinal products.

Iodinated contrast agents
Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin hydrochloride accumulation and an increased risk of lactic acidosis.

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 functioning 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 diabetes is not treated with metformin but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus.

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, breastfeeding is not recommended during metformin treatment. A decision on whether to discontinue breast-feeding should be made, taking into account the benefit of breast-feeding and the potential risk to adverse effects on the child.

Fertility
Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600mg/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 (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 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000) to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Metabolism and nutrition disorders:	
Very rare:	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 megaloplastic anaemia. 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 HPRA Pharmacovigilance Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: http://www.hpra.ie/; e-mail: medsafety@hpra.ie

4.9 Overdose

Hypoglycaemia has not been seen with metformin 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

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

Mechanism of action
Metformin hydrochloride may act via 3 mechanisms:
(1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
(2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
(3) and delay of intestinal glucose absorption.

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin hydrochloride increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

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

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

Clinical efficacy and safety
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 hydrochloride after failure of diet alone showed:
- a significant reduction of the absolute risk of any diabetes-related complication in the metformin hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride used as second-line therapy, in combination with a sulfonylurea.

In type 1 diabetes, the combination of metformin hydrochloride 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 tablet, maximum plasma concentration (Cmax) 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 hydrochloride absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin hydrochloride absorption is non-linear.

At the recommended metformin hydrochloride 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 hydrochloride 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 hydrochloride 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.

Biotransformation:

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

Elimination:
Renal clearance of metformin hydrochloride is > 400 ml/min, indicating that metformin hydrochloride 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 hydrochloride 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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Povidone K-30

Magnesium stearate

Film-coat:

Hypromellose

Hydroxypropyl cellulose

Macrogol 400 and 8000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Metformin Mylan tablets are packed in blister packs (PVC Aluminium) containing 10, 15, 20, 28, 30, 40, 50, 56, 60, 84, 90, 100, 120 and 180 tablets and bottles (high density polyethylene) with caps (polypropylene) containing 30, 100, 180, 200, 300, 400, 500 and 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd t/a Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0577/132/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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