SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metformin Hydrochloride Brown & Burk 1000 mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 1000 mg metformin hydrochloride equivalent to 780 mg metformin base.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release Tablet.

White to off white, capsule shaped, biconvex tablets, debossed on one side with '1000' and on the other side plain. The tablets are approximately 22.6 mm in length and 10.6 mm in breadth.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Reduction in the risk or delay of the onset of type 2 diabetes mellitus in adults, 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 despite implementation of intensive lifestyle change for 3 to 6 months

  Treatment with Metformin Hydrochloride Prolonged-release Tablets must be based on a risk score incorporating appropriate measures of glycaemic control and including evidence of high cardiovascular risk (see section 5.1).

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

4.2 Posology and method of administration

Posology

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

Reduction in the risk or delay of the onset of type 2 diabetes

- Metformin should only be considered where intensive lifestyle modifications for 3 to 6 months have not resulted in adequate glycaemic control.
- The therapy should be initiated with one tablet of Metformin Hydrochloride Prolonged-release Tablets 500 mg once daily with the evening meals.
- 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 gastrointestinal tolerability. The maximum recommended dose is 4 tablets (2000 mg) once daily with the evening meal.
- It is recommended to regularly monitor (every 3-6 months) the glycaemic status (OGTT and/or FPG and/or HbA1c value) as well as the risk factors to evaluate whether treatment needs to be continued, modified or discontinued.
- A decision to re-evaluate therapy is also required if the patient subsequently implements improvements to diet and/or exercise, or if changes to the medical condition will allow increased lifestyle interventions to be possible.

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

- The usual starting dose is one tablet of Metformin Hydrochloride Prolonged-release Tablets 500 mg once daily.
- After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dose is 4 tablets daily.
- Dosage increases should be made in increments of 500 mg every 10- 15 days, up to a maximum of 2000 mg once daily with the evening meal. If glycaemic control is not achieved on Metformin Hydrochloride Prolonged-release Tablets 2000 mg once daily, Metformin Hydrochloride Prolonged-release Tablets 1000 mg twice daily should be considered, with both doses being given with food. If glycaemic control is still not achieved, patients may be switched to standard metformin hydrochloride tablets to a maximum dose of 3000 mg daily.
- In patients already treated with Metformin Tablets, the starting dose of Metformin Hydrochloride Prolonged-release Tablets should be equivalent to the daily dose of metformin immediate release tablets. In patients treated with metformin hydrochloride at a dose above 2000 mg daily, switching to Metformin Hydrochloride Prolonged-release Tablets is not recommended.
- If transfer from another oral antidiabetic is intended: discontinue the other agent and initiate Metformin Hydrochloride Prolonged-release Tablets at the dose indicated above.
- Metformin Hydrochloride Prolonged-release Tablets 750 mg and Metformin Hydrochloride Prolonged-release Tablets 1000 mg are intended for patients who are already treated with Metformin tablets (prolonged or immediate release).
- The dose of Metformin Hydrochloride Prolonged-release Tablets 750 mg or Metformin Hydrochloride Prolonged-release Tablets 1000 mg should be equivalent to the daily dose of Metformin tablets (prolonged or immediate release), up to a maximum dose of 1500 mg or 2000 mg respectively, given with the evening meal.

Combination with insulin

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

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

Elderly:

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

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

Renal impairment:

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

GFR (mL/min)	Total maximum daily dose	Additional considerations
60-89	2000 mg	Dose reduction may be considered in relation to declining renal function.
45-59	2000 mg	Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose.
30-44	1000 mg	
<30	-	Metformin is contraindicated.

Paediatric population:

In the absence of available data, Metformin Prolonged-release Tablets should not to be used in children.

Method of Administration:

Swallow the tablets whole with a glass of water. Do not chew.

4.3 Contraindications

- Hypersensitivity to metformin or to any of the excipients listed insection 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 diseases, 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 is 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 (above 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).

Elderly:

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

Administration of iodinated contrast agent:

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 section 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.

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 never causes hypoglycaemia, although caution is advised when it is used in combination with insulin and other oral antidiabetic (e.g. sulfonylureas or meglitinides).

The tablet shells may be present in the faeces. Patients should be advised that this is normal.

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 Hydrochloride Brown & Burk contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per prolonged-release tablet, that is to say essentially ‘sodium-free’.

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 insufficiency

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 section 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 other drug 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, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

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

4.6 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, preclampsia, 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.

ssssssssssssssBreast-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 effect 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 meglinitides).

4.8 Undesirable effects

In post marketing data and in controlled clinical studies, adverse event reporting in patients treated with Metformin Prolonged-release Tablets was similar in nature and severity to that reported in patients treated with Metformin Hydrochloride immediate release tablets.

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

The following adverse reactions may occur with Metformin Hydrochloride Prolonged-release Tablets.

Frequencies are defined as follows: very common: >1/10; common ≥1/100, <1/10; uncommon ≥1/1000, <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 Special warnings and precautions for use).

Nervous system disorders:

Common:

- Taste disturbance

Gastrointestinal disorders:

Very common:

- Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders:

Very rare:

- Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders:

Very rare:

- Skin reactions such as erythema, pruritus, urticarial

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal products 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ORAL ANTI-DIABETICS

(A10BA02: Gastrointestinal tract and metabolism)

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

Mechanism of action

Metformin may act via 3 mechanisms:

1. reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.

2. in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation.

3. and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

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

Pharmacodynamic effects

In clinical studies, the major non glycemic effect of metformin is either weight stability or modest weight loss.

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

Clinical Efficacy:

Reduction in the risk or delay of type 2 diabetes mellitus

The **Diabetes Prevention Program** (DPP) was a multicenter randomised controlled clinical trial in adults assessing the efficacy of an intensive lifestyle intervention or metformin to prevent or delay the development of type 2 diabetes mellitus.

Inclusion criteria were age ≥25 years, BMI ≥24 kg/m^2 (≥22 kg/m^2 for Asian-Americans), and impaired glucose tolerance plus a fasting plasma glucose of 95 – 125 mg/dl (or ≤125 mg/dl for American Indians). Patients were either treated with intensive lifestyle intervention, 2x850 mg metformin plus standard lifestyle change, or placebo plus standard lifestyle change.

The mean baseline values of the DPP participants (n=3,234 for 2.8 years) were age 50.6± 10.7 years, 106.5±8.3 mg/dl fasted plasma glucose, 164.6±17.0 mg/dl plasma glucose two hours after an oral glucose load, and 34.0±6.7 kg/m^2 BMI. Intensive lifestyle intervention as well as metformin significantly reduced the risk of developing overt diabetes compared to placebo, 58% (95% CI 48-66%) and 31% (95% CI 17-43%), respectively.

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

The patients who benefited most from the metformin treatment were aged below 45 years, with a BMI equal or above 35kg/m^2, a baseline glucose 2 h value of 9.6-11.0 mmol/l, a baseline HbA_{1C} 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 HbA_{1C} are available.

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

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

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

Treatment of type 2 diabetes mellitus

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

- a significant reduction of the absolute risk of any diabetes-related complication in metformin group (29.8 events/1000 patients-years) versus diet alone (43.3 events/1000 patient-years), p= 0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (4.01 events/1000 patients-years), p=0.0034.
- a significant reduction of the absolute risk of the diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/1000 patient-year, p=0.017;
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1000 patient-years versus diet alone 20.6 events/1000 patient-years (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1000 patient-years (p = 0.021);
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1000 patient years, diet alone 18 events/1000 patients-years (p=0.01)

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

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

5.2 Pharmacokinetic properties

Absorption

After an oral dose of the Prolonged-release Tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a Tmax at 7 hours (Tmax for the immediate release tablet is 2.5 hours).

At steady state, similar to the immediate release formulation, Cmax and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000 mg of Metformin Prolonged-release Tablets is similar to that observed after administration of 1000 mg of metformin immediate release tablets b.i.d.

Intrasubject variability of Cmax and AUC of Metformin Prolonged-release Tablets is comparable to that observed with metformin immediate release tablets.

When the Prolonged-release Tablet is administered in fasting conditions the AUC is decreased by 30 % (both Cmax and Tmax are unaffected).

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

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

Following a single oral administration of 1500 mg of Metformin Hydrochloride Prolonged-release Tablets 750 mg, a mean peak plasma concentration of 1193 is achieved with a median time of 5 hours range of 4 to 12 hours.

Metformin Hydrochloride Prolonged-released Tablets 750 mg was shown to be bioequivalent to Metformin Hydrochloride Prolonged-release Tablets 500 mg at a 1500 mg dose with respect to Cmax and AUC in healthy fed and fasting subjects.

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

Metformin Hydrochloride Prolonged-release Tablets 1000 mg was shown to be bioequivalent to Metformin Hydrochloride Prolonged-release Tablets 500 mg at a 1000 mg dose with respect to Cmax and AUC in healthy fed and fasted subjects.

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

Distribution

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

Metabolism:

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

Elimination

Renal clearance of metformin is >400ml/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).

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K-90F

Colloidal Anhydrous Silica

Carmellose sodium

Hypromellose 90SH

Microcrystalline Cellulose

Magnesium Stearate

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

The tablets are available in blister strips [Clear PVC Film, coated with PVdC and Aluminium Foil].

Pack size:
14, 20, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 180 or 600 tablets in blister.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 25298/0229

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