SUMMARY OF PRODUCT CHARACTERISTICS

1 Name of the medicinal product

1.1.Product Name : PANFOR PR-500 (Metformin Hydrochloride 500 mg Prolonged Release Tablets)

1.2 Strength : 500 mg

1.3 Pharmaceutical Dosage Form : Oral Tablets

2. Qualitative and Quantitative composition

Name of Ingredient	Specification	mg per tablet	Qty (Batch/Kg)	Function
Dry Mixing				
Metformin Hydrochloride[1]	Ph.Eur	500.000	462.500	Active
Hypromellose (K100M)	Ph.Eur	186.700	172.698	Release controlling agent
Carboxy-methylcellulose Sodium (Sodium CMC)[2]	Ph.Eur	233.300	215.803	Diluent
Purified Water[3]	USP/Ph.Eur	q.s	-	Granulating vehicle
Lubrication				
Magnesium Stearate	Ph.Eur	5.0	4.625	Lubricant
Total weight (Per tablet)		**925.000**	**855.625**	

3. Pharmaceutical Form

Prolonged release tablet

4. Clinical Particulars

4.1 Therapeutic indications.

• Reduction in the risk or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with IGT*(Impaired Glucose Tolerance) and/or IFG*(Impaired Fasting Glucose), and/or increased HbA1C who are:

✓ at high risk for developing overt type 2 diabetes mellitus and

✓ still progressing towards type 2 diabetes mellitus despite implementation of intensive lifestyle change for 3 to 6 months.

Treatment with metformin prolonged release tablet must be based on a risk score incorporating appropriate measure of glycaemic control and including evidence of high cardiovascular risk.

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

*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 PR may be used as monotherapy or in combination with other oral antidiabetic agent, 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 Metformin 500 mg once daily with the evening meal.

• After 10 to 15 days dose adjustment on the basis of blood glucose measurements is recommended (OGTT and/or FPG and/or HbA1C values to be within the normal range). A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended 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 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 500mg every 10-15 days, up to a maximum of 2000mg once daily with the evening meal. If glycaemic control is not achieved on Metformin 2000mg once daily, Metformin 1000mg twice daily should be considered, with both doses being given with food. If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.

• In patients already treated with metformin tablets, the starting dose of Metformin should be equivalent to the daily dose of metformin immediate release tablets. In patients treated with metformin at a dose above 2000 mg daily, switching to Metformin is not recommended.

• If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate Metformin at the dose indicated above.

• Metformin 750 mg and Metformin 1000 mg are intended for patients who are already treated with metformin tablets (prolonged or immediate release).
• The dose of Metformin 750 mg or Metformin 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 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 750 mg or Metformin 1000 mg should be equivalent to the daily dose of metformin tablets up to a 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 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.

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 and metformin initiation is therefore not recommended in these patients.

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 should not be used in children.

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 special 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.

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Renal function:

GFR should be assessed before treatment initiation and regularly thereafter, Metformin is contraindicated in patients with GFR<30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function.

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

Elderly:

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

Administration of iodinated contrast agents:

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

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 or other oral antidiabetics (e.g. sulphonylureas or meglitinides).

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

4.5 Interaction with other medicinal products and other forms of 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.

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.

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 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 fetal development, parturition or postnatal development.

When the patient plans to become pregnant and during pregnancy, it is recommended that impaired glycaemic control or diabetes are not treated with metformin. For diabetes it is recommended that insulin should 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 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. sulphonylureas, insulin, or meglinitides).

4.8 Undesirable effects

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

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.

Frequencies are defined as follows: very common: >1/10; common ≥1/100, <1/10; uncommon ≥1/1,000, <1/100; rare ≥1/10,000, <1/1,000; very rare <1/10,000.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders

Very rare:

• Lactic acidosis.

• Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such an aetiology is recommended if a patient presents with megaloblastic anaemia.

Nervous system disorders

Common:

• Taste disturbance

Gastrointestinal disorders

Very common:

• Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. 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

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 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

Mechanism of action

ORAL ANTIDIABETICS

(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:

• reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation 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).

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 T_{max} at 7 hours (T_{max} for the immediate release tablet is 2.5 hours).

At steady state, similar to the immediate release formulation, C_{max} and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000mg of metformin prolonged release tablets is similar to that observed after administration of 1000mg of metformin immediate release tablets b.i.d.

Intrasubject variability of C_{max} and AUC of metformin prolonged release 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 C_{max} and T_{max} 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 2000mg of metformin as prolonged release tablets.

Following a single oral administration of 1500 mg of Metformin 750 mg, a mean peak plasma concentration of 1193 ng/ml is achieved with a median value of 5 hours and a range of 4 to 12 hours.

Metformin 750 mg was shown to be bioequivalent to Metformin 500 mg at a 1500 mg dose with respect to C_{max} and AUC in healthy fed and fasted subjects.

Following a single oral administration in the fed state of one tablet of Metformin 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 1000 mg was shown to be bioequivalent to Metformin 500 mg at a 1000 mg dose with respect to C_{max} 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% (C_{max} is increased by 26% and T_{max} 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 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.

5.3 Preclinical safety data

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

6. Pharmaceutical particulars

6.1 List of excipients:

Name of Ingredient	Quality Standard
Hypromellose K100M	Ph. Eur.
Carboxymethylcellulose Sodium (Sodium CMC)	Ph. Eur.
Purified Water	Ph. Eur.
Magnesium Stearate	Ph. Eur.

6.2 Incompatibilities: None.

6.3 Shelf life: 24 months

6.4 Special precautions for storage

Keep out of reach of children

Protect from light & moisture

Store below 30°C in a dry place

Swallow whole, do not chew or crush the tablet

6.5 Nature and contents of container.

Blister pack of 10 Tablets (Printed Aluminium Foil 0.025 mm and PVC/PVDC film 90 gsm - DMF grade) 10 such blisters in a carton.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. Marketing authorization holder

MEGA LIFESCIENCES Public Company Limited, Thailand.

8 Marketing authorization number

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9 Date of first registration

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10 Date of revision of the text

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