SUMMARY OF PRODUCT CHARACTERISTICS

PRODUCT INFORMATION FOR HEALTH PROFESSIONALS

1. NAME OF MEDICINAL PRODUCT:

Diamet SR 500; 1000 Tablet (Metformin Hydrochloride)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each tablet contains		
Metformin Hydrochloride	500mg	; 1000mg
Excipients	q.s	q.s

3. PHARMACOLOGICAL FORM:

Tablet

4. CLINICAL PARTICULARS:

4.1 THERAPUETIC INDICATIONS:

Reduction in the risk or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with IGT* and/or IFG*, and/or increased HbA1C who are:

- At high risk for developing overt type 2 diabetes mellitus (see section 5.1) and

- Still progressing towards type 2 diabetes mellitus despite implementation of intensive lifestyle change for 3 to 6 months

Treatment with Diamet SR 500 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 modifications should be continued when metformin is initiated, unless the patient is unable to do so because of medical reasons.

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

• 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. Diamet SR may be used as monotherapy or in combination with other oral anti diabetic agents, or with insulin.

4.2 DOSAGE AND 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 Diamet SR 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 Diamet SR 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 Diamet SR 2000mg once daily, Diamet SR 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 Diamet SR 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 Diamet SR is not recommended.

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

• Diamet SR 750 mg and Glucophage SR 1000 mg are intended for patients who are already treated with metformin tablets (prolonged or immediate release).

• The dose of Glucophage SR 750 mg or Glucophage SR 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 Glucophage SR 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 Glucophage SR 750 mg or Glucophage SR 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 (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, Glucophage SR should not be used in children.

4.3 CONTRA-INDICATION:

Metformin is contraindicated in patients with:

- Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction and septicemia.
- Known hypersensitivity to metformin.

- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

Metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

4.4 SPECIAL WARNINGS AND PRECAUTIONS

Monitoring Of Renal Function

Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive Metformin. In patients with advanced age, Metformin should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those ≥ 80 years of age, renal function should be monitored regularly and, generally, Metformin should not be titrated to the maximum dose.

Before initiation of Metformin therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and Metformin discontinued if evidence of renal impairment is present.

Use of concomitant medications that may affect renal function or metformin disposition- Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion, should be used with caution.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials) - Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, Metformin should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been reevaluated and found to be normal.

Hypoxic states - Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on Metformin therapy, the drug should be promptly discontinued.

Surgical procedures - Metformin therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol intake - Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving Metformin.

Impaired hepatic function - Since impaired hepatic function has been associated with some cases of lactic acidosis, Metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B12 levels - In controlled clinical trials of metformin in 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on Metformin and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate Vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B12 levels. In these patients, routine serum Vitamin B12 measurements at two- to three-year intervals may be useful.

Change in clinical status of patients with previously controlled type 2 diabetes - A patient with type 2 diabetes previously well controlled on Metformin who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, Metformin must be stopped immediately and other appropriate corrective measures initiated.

Hypoglycemia - Hypoglycemia does not occur in patients receiving Metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during

concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Loss of control of blood glucose - When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold Metformin and temporarily administer insulin. Metformin may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with Metformin or sulfonylurea monotherapy, combined therapy with Metformin and sulfonylurea may result in a response. Should secondary failure occur with combined Metformin /sulfonylurea therapy, it may be necessary to consider therapeutic alternatives including initiation of insulin therapy.

4.5 DRUG INTERACTION:

Glyburide

In a single-dose interaction study in type 2 diabetes patients, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and Cmax were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamics effects make the clinical significance of this interaction uncertain.

Furosemide

A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood Cmax by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the Cmax and AUC of furosemide were

31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin Cmax and AUC by 20%, respectively, and increased the amount excreted in the urine. Tmax and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic Drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of metformin and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Metformin, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving Metformin, the patient should be observed closely for hypoglycemia.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

4.6 EFFECT ON ABILITY TO DRIVE AND USE MACHINES:

Metformin hydrochloride monotherapy does not cause hypo glycaemia 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 meformin hydrochloride is used in combination with other antidiabetic agents (sulfonylureas, insulin or meglitinides).

4.7 SIDE EFFECTS / ADVERSE EFFECTS

During treatment initiation, the most common side effects 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.

4.8 Undesirable effects

The following adverse reactions may occur under treatment with metformin. Frequencies are defined as follows: very common: ≥1/10; common ≥1/100, <1/10; uncommon ≥1/1,000, <1/100; rare ≥1/10,000, <1/1,000; very rare <1/10,000. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders:

very rare:

Lactic acidosis

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

Nervous system disorders:

Common: Taste disturbance

Gastrointestinal disorders:

very common: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders:

very rare: Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders:

very rare: Skin reactions such as erythema, pruritus, urticaria

Paediatric population

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

4.9 OVER DOSAGE:

Overdoses with metformin are rare, but may result in serious consequences. Hypoglycemia has not been seen even with ingestion of up to 85 grams of metformin although lactic acidosis has occurred in such circumstances. The intake of 35 g of metformin has shown to be lethal, the maximum reported tolerated exposure was in a 70 year-old diabetic patient who ingested 63 grams of metformin. Overdose of metformin has occurred, including ingestion of amounts greater than 50g.

Experience with over dosage, deliberate or accidental and its treatment: Symptom associated with Metformin overdose is lactic acidosis with nonspecific symptoms that includes severe nausea, vomiting, diarrhea, epigastric pain, thirstiness, lost appetite, lethargy and hyperpnoea. Hypotension, hypothermia, acute renal failure, coma and cardiac arrest also represent significant clinical features. Treatment of metformin overdose is generally supportive, as no specific antidote is known. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

Current treatment approach of the metformin overdose associated lactic acidosis is volume expansion, intravenous application of sodium bicarbonate, intermittent hemodialysis and high volume continuous venovenous hemodiafiltration with a bicarbonate substitute.

Metformin overdose should be directed with regular monitoring of renal function. Hemodialysis has an important role in and removal of the metformin from the circulation, preventing in turn further acidosis. Hemofiltration is the preferable option for patients who are hemodynamically unstable to tolerate hemodialysis.

5. PHARMACOLOGY PROPERTIES:

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Anti-diabetic, ATC code: A10BA02

Mechanism of action: 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 hypoglycemia.

Metformin hydrochloride may act via 3 mechanisms:

- Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization
- And delay of intestinal glucose absorption.

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

5.1 Pharmacokinetic properties

Absorption

After an oral dose of metformin hydrochloride 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 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 4 microgram/ml, even at maximum doses.
Food decreases the extent and slightly delays the absorption of metformin hydrochloride. Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC (area under the curve) and a 35 minute prolongation of 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.

Metabolism/Excretion

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.

6. PHARMACEUTICAL PARTICULARS:

6.1 LIST OF EXCIPIENTS:

Metformin HCL BP
Sodium CMC
HPMC K 100
Magnesium Stearate
Aerosil

6.2 INCOMPATIBILITIES:

Not Applicable

6.3 SHELF LIFE:

36 Months

6.4 SPECIAL PRECAUTION FOR STORAGE:

Store below 30°C in a dry place. Protect from light.

6.5 NATURE AND CONTENT OF CONTAINER:

The product is supplied in blister packs (clear PVC/Aluminum), each blister containing
6 x 14 tablets.

6.6 SPECIAL PRECAUTION FOR DISPOSAL:

To be destroyed by NAFDAC enforcement unit.