SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE PRODUCT

Gpride® (Glimepiride) 1mg Tablets

Gpride® (Glimepiride) 2mg Tablets

Gpride® (Glimepiride) 4mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Gpride® 1mg Tablets	Gpride® 2mg Tablets	Gpride® 4mg Tablets
Each tablet contains:	Each tablet contains:	Each tablet contains:
Glimepiride USP.....1mg	Glimepiride USP.....2mg	Glimepiride USP.....4mg

3. PHARMACEUTICAL FORM

Tablet

Appearance:

Gpride® 1mg Tablets: Light green color, capsular shaped tablets having break line on one side and engraved "SAMI" on the other side.
Gpride® 2mg Tablets: Pink color, capsular shaped tablets having break line on one side and engraved "SAMI" on the other side.
Gpride® 4mg Tablets: Blue color, capsular shaped tablets having break line on one side and engraved "SAMI" on the other side.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

Gpride® is indicated for the treatment of type 2 diabetes mellitus, when diet, physical exercise, and weight reduction alone are not adequate.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

For oral administration. The basis for successful treatment of diabetes is a good diet, regular physical activity, as well as routine checks of blood and urine. Tablets or insulin cannot compensate if the patient does not keep to the recommended diet.

Posology:

Dose is determined by the results of blood and urinary glucose determinations. The starting dose is 1mg glimepiride per day. If good control is achieved this dose should be used for maintenance therapy. For the different dose regimens appropriate strengths are available. If control is unsatisfactory the dose should be increased, based on the glycaemic control, in a stepwise manner with an interval of about 1 to 2 weeks between each step, to 2, 3, or 4mg glimepiride per day. A dose of more than 4mg glimepiride per day gives better results only in exceptional cases. The maximum recommended dose is 6mg glimepiride per day. In patients not adequately controlled with the maximum daily dose of metformin, concomitant glimepiride therapy can be initiated. While maintaining the metformin dose, the glimepiride therapy is started with a low dose, and is then titrated up depending on the desired level of metabolic control up to the maximum daily dose. The combination therapy should be initiated under close medical supervision. In patients not adequately controlled with the maximum daily dose of glimepiride, concomitant insulin therapy can be initiated if necessary. While maintaining the glimepiride dose, insulin treatment is started at low dose and titrated up depending on the desired level of metabolic control. The combination therapy should be initiated under close medical supervision. Normally a single daily dose of glimepiride is sufficient. It is recommended that this dose be taken shortly before or during a substantial breakfast or - if none is taken - shortly before or during the first main meal. If a dose is forgotten, this should not be corrected by increasing the next dose. If a patient has a hypoglycaemic reaction on 1mg glimepiride daily, this indicates that they can be controlled by diet alone. In the course of treatment, as an improvement in the control of diabetes is associated with higher insulin sensitivity, glimepiride requirements may fall. To avoid hypoglycemia timely dose reduction or cessation of therapy must therefore be considered. Change in dose may also be necessary if there are changes in weight or lifestyle of the patient, or other factors that increase the risk of hypo- or hyperglycemia.

Switch over from other oral hypoglycaemic agents to glimepiride: A switch over from other oral hypoglycaemic agents to glimepiride can generally be done. For the switch over to glimepiride the strength and the half-life of the previous medicinal product has to be taken into account. In some cases, especially in antidiabetics with a long half-life (e.g. chlorpropamide), a wash out period of a few days is advisable in order to minimize the risk of hypoglycaemic reactions due to the additive effect. The recommended starting dose is 1mg glimepiride per day. Based on the response the glimepiride dose may be increased stepwise, as indicated earlier.

Switch over from insulin to glimepiride: In exceptional cases, where type 2 diabetic patients are regulated on insulin, a changeover to glimepiride may be indicated. The changeover should be undertaken under close medical supervision.

Special populations: In case of severe renal or hepatic function disorders, a changeover to insulin is required.

Paediatric population: There are no data available on the use of glimepiride in patients under 8 years of age. For children aged 8 to 17 years, there are limited data on glimepiride as monotherapy. The available data on safety and efficacy are insufficient in the paediatric population and therefore such use is not recommended.

Method of administration:

Tablets should be swallowed without chewing with some liquid.

4.3. CONTRAINDICATIONS:

Glimepiride is contraindicated in patients with the following conditions:

- Hypersensitivity to glimepiride, other sulfonylureas or sulfonamides or to any of the excipients.
- Diabetes mellitus type I
- Diabetic coma
- Ketoacidosis
- Severe renal or hepatic function disorders. In case of severe renal or hepatic function disorders, a change over to insulin is required.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Glimepiride must be taken shortly before or during a meal: When meals are taken at irregular hours or skipped altogether, treatment with glimepiride may lead to hypoglycemia. Possible symptoms of hypoglycemia include headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, alertness and reaction time, depression, confusion, speech and visual disorders, aphasia, tremors, paresis, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, somnolence and loss of consciousness up to and including coma, shallow respiration and bradycardia. In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris, and cardiac arrhythmias: The clinical picture of a severe hypoglycemic attack may resemble that of a stroke. Symptoms can almost always be promptly controlled by immediate intake of carbohydrates (sugar). Artificial sweeteners have no effect. It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycemia may recur. Severe hypoglycemia or prolonged hypoglycemia, only temporarily controlled by the usual amounts of sugar, requires immediate medical treatment and occasionally hospitalization.

Factors favoring hypoglycemia include:

- unwillingness or (more commonly in older patients) incapacity of the patient to cooperate
- undernutrition, irregular mealtimes or missed meals, or periods of fasting
- alterations in diet
- an imbalance between physical exertion and carbohydrate intake
- consumption of alcohol; especially in combination with skipped meals
- impaired renal function
- serious liver dysfunction
- overdose with glimepiride
- certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter-regulation of hypoglycemia (as for example in certain disorders of thyroid function and in anterior pituitary or adrenocortical insufficiency)
- concurrent administration of certain other medicinal products.

Treatment with glimepiride requires regular monitoring of glucose levels in blood and urine. In addition, determination of the proportion of glycosylated haemoglobin is recommended. Regular hepatic and haematological monitoring (especially leucocytes and thrombocytes) is required during treatment with glimepiride. In stressful situations (e.g. accidents, acute operations, infections with fever, etc.), a temporary switch to insulin may be indicated. No experience has been gained concerning the use of glimepiride in patients with severe impairment of liver function or dialysis patients. In patients with severe impairment of renal or liver function change over to insulin is indicated. Treatment of patients with G6PD deficiency with sulfonylurea agents can lead to haemolytic anemia. Since glimepiride belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered.

Gpride® contains lactose monohydrate: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Gpride® 1mg contains Apple green lake color, Gpride® 2mg contains Erythrosine lake color and Tartrazine yellow lake color and Gpride® 4mg contains Brilliant blue lake color and Erythrosine lake color: May cause allergic reactions.

This medicine contains less than 1mmol sodium (23mg) per tablet, that is to say essentially 'sodium-free'.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

If glimepiride is taken simultaneously with certain other medicinal products, both undesired increases and decreases in the hypo-glycaemic action of glimepiride can occur. For this reason, other medicinal products should only be taken with the knowledge (or at the prescription) of the doctor. Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is known to be influenced by the concomitant administration of CYP2C9 inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole). Results from an in vivo interaction study reported in the literature show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors. Based on the experience with glimepiride and with other sulfonylureas the following interactions have to be mentioned. Potentiation of the blood-glucose-lowering effect and, thus, in some instances, hypoglycemia may occur when one of the following medicinal products is taken, for example:

- phenylbutazone, azapropazone and oxyfenbutazone,
- insulin and oral antidiabetic products, such as metformin,

- salicylates and p-amino-salicylic acid,
- anabolic steroids and male sex hormones,
- chloramphenicol, certain long-acting sulfonamides, tetracyclines, quinolone antibiotics and clarithromycin,
- coumarin anticoagulants,
- fenfluramine,
- disopyramide,
- fibrates,
- ACE-inhibitors,
- fluoxetine, MAO inhibitors,
- allopurinol, probenecid, sulfinpyrazone,
- sympatholytic,
- cyclophosphamide, trophosphamide and iphosphamides,
- miconazole, fluconazole,
- pentoxifylline (high dose parenteral),
- tritoqualine.

Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following medicinal products is taken, for example:

- oestrogens and progestogens,
- saluretics, thiazide diuretics,
- thyroidstimulating agents, glucocorticoids,
- phenothiazine derivatives, chlorpromazine,
- adrenaline and sympathomimetics,
- nicotinic acid (high doses) and nicotinic acid derivatives,
- laxatives (long-term use),
- phenytoin, diazoxide,
- glucagon, barbiturates and rifampicin,
- acetazolamide.

H_2-antagonists, beta-blockers, clonidine, and reserpine may lead to either potentiation or weakening of the blood–glucose–lowering effect. Under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation to hypoglycemia may be reduced or absent. Alcohol intake may potentiate or weaken the hypoglycemic action of glimepiride in an unpredictable fashion. Glimepiride may either potentiate or weaken the effects of coumarin derivatives. Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastrointestinal tract. No interaction was observed when glimepiride was taken at least for 4 hours before colesevelam. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

4.6. FERTILITY, PREGNANCY AND LACTATION

Fertility: No data on fertility is available.

Pregnancy: ***Risk related to the diabetes:*** Abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities and perinatal mortality. So, the blood glucose level must be closely monitored during pregnancy in order to avoid the teratogenic risk. The use of insulin is required under such circumstances. Patients who consider pregnancy should inform their physician. ***Risk related to glimepiride:*** There are no adequate data from the use of glimepiride in pregnant women. Animal studies have shown reproductive toxicity which likely was related to the pharmacologic action (hypoglycaemia) of glimepiride. Consequently, glimepiride should not be used during the whole pregnancy. In case of treatment by glimepiride, if the patient plans to become pregnant or if a pregnancy is discovered, the treatment should be switched as soon as possible to insulin therapy.

Breast-feeding: The excretion in human milk is unknown. Glimepiride is excreted in rat milk. As other sulfonylureas are excreted in human milk and because there is a risk of hypoglycaemia in nursing infants, breast-feeding is advised against during treatment with glimepiride.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

No studies on the effects on the ability to drive and use machines have been performed. The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery). Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or operate machinery in these circumstances.

4.8. UNDESIRABLE EFFECTS:

The following adverse reactions from clinical investigations were based on experience with glimepiride and other sulfonylureas, were listed below by system organ class and in order of decreasing incidence (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).

Blood and lymphatic system disorders: ***Rare:*** Thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, erythropenia, haemolytic anaemia and pancytopenia[1]. ***Not known:*** Severe thrombocytopenia with platelet count less than 10,000/µl and thrombocytopenic purpura.

Immune system disorders: ***Very rare:*** Leukocytoclastic vasculitis. Mild hypersensitivity reactions that may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock. ***Not known:*** Cross-allergenicity with sulphonylureas, sulphonamides or related substances is possible.

Metabolism and nutrition disorders: ***Rare:*** Hypoglycaemia[2].

Eye disorders: ***Not known:*** Visual disturbances[3].

Gastrointestinal disorders: ***Rare:*** Dysgeusia. ***Very rare:*** Nausea, vomiting, diarrhoea, abdominal distension, abdominal discomfort and abdominal pain[4].

Skin and subcutaneous tissue disorders: ***Rare:*** Alopecia. ***Not known:*** Hypersensitivity reactions of the skin may occur as pruritus, rash, urticaria and photosensitivity.

Hepatobiliary disorders: ***Very rare:*** Hepatic function abnormal (e.g. with cholestasis and jaundice), hepatitis and hepatic failure. ***Not known:*** Hepatic enzymes increased.

Investigations: ***Rare:*** Weight pain. ***Very rare:*** Blood sodium decrease.

[1] These alterations are in general reversible upon discontinuation of treatment.

[2] These hypo-glycaemic reactions mostly occur immediately, may be severe and are not always easy to correct. The occurrence of such reactions depends, as with other hypo-glycaemic therapies, on individual factors such as dietary habits and dose.

[3] These disturbances are transient and may occur especially on initiation of treatment, due to changes in blood glucose levels.

[4] These reactions seldom lead to discontinuation of therapy.

4.9. OVERDOSE:

Symptoms: After ingestion of an overdose, hypo-glycaemia may occur, lasting from 12 to 72 hours, and may recur after an initial recovery. Symptoms may not be present for up to 24 hours after ingestion. In general observation in the hospital is recommended. Nausea, vomiting, and epigastric pain may occur. The hypo-glycemia may, in general, be accompanied by neurological symptoms like restlessness, tremor, visual disturbances, coordination problems, sleepiness, coma and convulsions.

Management: Treatment primarily consists of preventing absorption by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbent) and sodium sulphate (laxative). If large quantities have been ingested, gastric lavage is indicated, followed by activated charcoal and sodium sulphate. In case of (severe) overdose hospitalization in an intensive care department is indicated. Start the administration of glucose as soon as possible, if necessary, by a bolus intravenous injection of 50ml of a 50% solution, followed by an infusion of a 10% solution with strict monitoring of blood glucose. Further treatment should be symptomatic. In particular, when treating hypoglycemia due to accidental intake of glimepiride in infants and young children, the dose of glucose given must be carefully controlled to avoid the possibility of producing dangerous hyperglycemia. Blood glucose should be closely monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Blood glucose lowering drugs, excl. insulins: Sulfonylureas. **ATC code:** A10BB12.

Glimepiride is an orally active hypoglycemic substance belonging to the sulfonylurea group. It may be used in non-insulin dependent diabetes mellitus. Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells. As with other sulfonylureas, this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects also postulated for other sulfonylureas.

Mechanism of action: Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells. As with other sulfonylureas, this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects also postulated for other sulfonylureas.

5.2. PHARMACOKINETICS:

Absorption: The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only the absorption rate is slightly diminished. Maximum serum concentrations (C_{max}) are reached approx. 2.5 hours after oral intake (mean 0.3µg/ml during multiple dosing of 4mg daily) and there is a linear relationship between dose and both C_{max} and AUC (area under the time/concentration curve).

Distribution: Glimepiride has a very low distribution volume (approx. 8.8 liters) which is roughly equal to the albumin distribution space, high protein binding (> 99%), and a low clearance (approx. 48ml/min). In animals, glimepiride is excreted in milk. Glimepiride is transferred to the placenta. Passage of the blood-brain barrier is low.

Biotransformation and Elimination: The mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After high doses, slightly longer half-lives were noted. After a single dose of radio-labeled glimepiride, 58% of the radioactivity was recovered in the urine, and 35 % in the faeces. No unchanged substance was detected in the urine. Two metabolites – most probably resulting from hepatic metabolism (major enzyme is CYP2C9) – were identified both in urine and faeces: the hydroxy derivative and the carboxy derivative. After oral administration of glimepiride, the terminal half-lives of these metabolites were 3 to 6 and 5 to 6 hours respectively. Comparison of single and multiple once-daily dosing revealed no significant differences in pharmacokinetics, and the intraindividual variability was very low. There was no relevant accumulation.

SUMMARY OF PRODUCT CHARACTERISTICS

5.3. PRECLINICAL SAFETY DATA:
Preclinical effects observed occurred at exposures sufficiently in excess of the maximum human exposure as to indicate little relevance to clinical use, or were due to the pharmacodynamic action (hypoglycemia) of the compound. This finding is based on conventional safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and reproduction toxicity studies. In the latter (covering embryotoxicity, teratogenicity, and developmental toxicity), adverse effects observed were considered to be secondary to the hypoglycaemic effects induced by the compound in dams and in offspring.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

Gpride® 1mg Tablets:
- Lactose monohydrate
- Microcrystalline cellulose
- Sodium starch glycolate
- Polyvinyl pyrrolidone
- Magnesium stearate
- Apple green lake color

Gpride® 2mg Tablets:
- Lactose monohydrate
- Microcrystalline cellulose
- Sodium starch glycolate
- Polyvinyl pyrrolidone
- Magnesium stearate
- Erythrosine lake color
- Tartrazine yellow lake color

Gpride® 4mg Tablets:
- Lactose monohydrate
- Microcrystalline cellulose
- Sodium starch glycolate
- Polyvinyl pyrrolidone
- Magnesium stearate
- Brilliant blue lake color
- Erythrosine lake color

6.2. INCOMPATIBILITIES:
Not applicable.

6.3. SHELF LIFE:
See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Avoid exposure to heat, light and humidity. Store between 15 to 30°C. Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:
Gpride® 1mg Tablets: Alu/Alu Blister, pack size 30's.
Gpride® 2mg Tablets: Alu/Alu Blister, pack size 30's.
Gpride® 4mg Tablets: Alu/Alu Blister, pack size 30's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:
Any unused product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:
USP Specs.

7. MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

8. MARKETING AUTHORISATION NUMBER(S)

Gpride® 1mg Tablets: 034051
Gpride® 2mg Tablets: 033008
Gpride® 4mg Tablets: 033009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Gpride® 1mg Tablets: 9th October, 2004
Gpride® 2mg Tablets: 10th July, 2004
Gpride® 4mg Tablets: 10th July, 2004

10. DATE OF REVISION OF THE TEXT

جی پرائیڈ ٹیبلٹ

(گلی میپیرائیڈ)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں

بچوں کی پہنچ سے دور رکھیں

دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ

کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی