# Summary of Product Characteristics

## 1. Name of the medicinal product
Gluco-Rite 5mg Tablets

## 2. Qualitative and quantitative composition
Glipizide 5 mg
Excipient with known effect:
Each tablet contains 153 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical form
Tablet.
White tablets, convex, scored with a break line on one side and with 'A' on the other side.

## 4. Clinical particulars
4.1 Therapeutic indications
Gluco-Rite is indicated as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with diabetes mellitus type II.

4.2 Posology and method of administration

PosologyAs for any hypoglycaemic agent, dosage must be adapted for each individual case.

Short term administration of glipizide may be sufficient during periods of transient loss of control in patients usually controlled well on diet.

In general, glipizide should be given shortly before a meal to achieve the greatest reduction in post-prandial hyperglycaemia.

Initial Dose

The recommended starting dose is 5 mg, given before breakfast or the midday meal. Mild diabetics, geriatric patients or those with liver disease may be started on 2.5 mg.

Titration

Dosage adjustments should ordinarily be in increments of 2.5 to 5 mg, as determined by blood glucose response. At least several days should elapse between titration steps. The maximum recommended single dose is 15 mg. If this is not sufficient, splitting the daily dosage may prove effective. Doses above 15 mg should ordinarily be divided.

Maintenance

Some patients may be effectively controlled on a once-a-day regimen. Total daily dosage above 15 mg should ordinarily be divided.

The maximum recommended daily dosage is 20 mg.

Paediatric population

Safety and effectiveness in children have not been established.

Use in Elderly and High Risk Patients

In elderly, debilitated and malnourished patients or patients with an impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycaemic reactions (see Initial Dose section 4.4).

Patients Receiving Other Oral Hypoglycaemic Agents

As with other sulphonylurea class hypoglycaemics, no transition period is necessary when transferring patients to glipizide. Patients should be observed carefully (1-2 weeks) for hypoglycaemia when being transferred from longer half-life sulphonylureas (e.g. chlorpropamide) to glipizide due to potential overlapping of drug effect.

Method of administration
For oral use only.

4.3 Contraindications

1. Hypersensitivity to the active substance glipizide, other sulphonylureas or sulphonamides, or to any of the excipients listed in section 6.1.

2. Insulin-dependent diabetes mellitus , diabetic ketoacidosis, diabetic coma;

3. Severe renal or hepatic insufficiency;

4. Patients treated with miconazole (see section 4.5);

5. Pregnancy and lactation

4.4 Special warnings and precautions for use

Glucose-6-phosphate dehydrogenase deficiency

Since glipizide belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency. Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to haemolytic anaemia and a non-sulfonylurea alternative should be considered.

Hypoglycaemia

All sulphonylurea agents are capable of producing severe hypoglycaemia. Renal or hepatic insufficiency may cause elevated blood levels of glipizide and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycaemic reactions. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycaemic action of glucose-lowering drugs.

Hypoglycaemia may be difficult to recognise in the elderly, and in people who are taking beta-adrenergic blocking drugs (see section 4.5.). Hypoglycaemia is more likely to occur when caloric- intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of control of blood glucose

When a patient stabilised on a diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue glipizide and administer insulin.

The effectiveness of any oral hypoglycaemic drug, including glipizide, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of diabetes or due to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

Renal and Hepatic Disease

The pharmacokinetics and/or pharmacodynamics of glipizide may be affected in patients with impaired renal or hepatic function. If hypoglycaemia should occur in such patients, it may be prolonged and appropriate management should be instituted.

Information for Patients

Patients should be informed of the potential risks and advantages of glipizide and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose.

The risks of hypoglycaemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Laboratory Tests

Blood and urine glucose should be monitored periodically. Measurement of glycosylated haemoglobin may be useful.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The following products are likely to increase the hypoglycaemic effect:

- **Contraindicated combinations**

*Miconazole*

Increase in hypoglycaemic effect, possibly leading to symptoms of hypoglycaemia or even coma.

- **Inadvisable combinations**

*Nonsteroidal Anti-inflammatory Drugs (e.g. phenylbutazone*) Increase in hypoglycaemic effect of sulphonylureas (displacement of sulphonylurea binding to plasma proteins and/or decrease in sulphonylurea elimination).

*Alcohol*

Increase in hypoglycaemic reaction which can lead to hypoglycaemic coma.

- **Combinations requiring precaution**

*Fluconazole*

Increase in the half-life of the sulphonylurea, possibly giving rise to symptoms of hypoglycaemia.

*Voriconazole*

Although not studied, voriconazole may increase the plasma levels of sulfonylureas, (e.g. tolbutamide, glipizide and glyburide) and therefore cause hypoglycaemia. Careful monitoring of blood glucose is recommended during co-administration.

*Salicylates (acetylsalicylic acid)*

Increase in hypoglycaemic effect by high doses of acetylsalicylic acid (hypoglycaemic action of the acetylsalicylic acid).

*Beta-blockers*

All beta-blockers mask some of the symptoms of hypoglycaemia, (i.e. palpitations and tachycardia). Most non cardio selective beta-blockers increase the incidence and severity of hypoglycaemia.

*Angiotensin converting Enzyme inhibitors*

The use of angiotensin converting enzyme inhibitors may lead to an increased hypoglycaemic effect in diabetic patients treated with sulphonylureas.

*Cimetidine*

The use of cimetidine may be associated with a reduction in post prandial blood glucose in patients treated with glipizide.

The hypoglycaemic action of sulphonylureas in general may also be potentiated by monoamine oxidase inhibitors, quinolones and drugs that are highly protein bound, such as sulfonamides, chloramphenicol, probenecid, coumarins and fibrates.

When such drugs are administered to (or withdrawn from) a patient receiving glipizide, the patient should be observed closely for hypoglycaemia (or loss of control).

The following products could lead to hyperglycaemia:

- **Inadvisable combinations**

*Danazol*

Diabetogenic effect of danazol. If it cannot be avoided, warn the patient and step up self monitoring of blood glucose and urine. Possibly adjust the dosage of antidiabetic agent during treatment with danazol and after its discontinuation.

- **Combinations requiring precaution**

*Colesevelam:* In studies assessing the effect of colesevelam on the pharmacokinetics of glipizide in healthy volunteers, reductions in glipizide AUC and Cmax of 12% and 13%, respectively were observed when colesevelam was coadministered with glipizide. When glipizide was administered 4 hours prior to colesevelam, there was no significant change in glipizide AUC or Cmax, -4% and 0%, respectively. Therefore, Gluco-Rite should be administered at least 4 hours prior to colesevelam to ensure that colesevelam does not reduce the absorption of glipizide.

*Phenothiazines (e.g. chlorpromazine) at High doses (> 100 mg /day of chlorpromazine)*

Elevation in blood glucose (reduction in insulin release).

*Corticosteroids*

Elevation in blood glucose.

*Sympathomimetics (e.g. ritodrine, salbutamol, terbutaline)*

Elevation in blood glucose due to beta-2-adrenoceptor stimulation.

*Progestogens*

Diabetogenic effects of high-dose progestogens. Warn the patient and step up self-monitoring of blood glucose and urine. Possibly adjust the dosage of antidiabetic agent during treatment with the neuroleptics, corticoids or progestogen and after discontinuation.

Other drugs that may produce hyperglycaemia and lead to a loss of control include the thiazides and other diuretics, thyroid products, oestrogens, oral contraceptives, phenytoin, nicotinic acid, calcium channel blocking drugs, and isoniazid.

When such drugs are administrated to (or withdrawn from) a patient receiving glipizide, the patient should be observed closely for hypoglycaemia.

4.6.Fertility, pregnancy and lactation

Pregnancy

Glipizide is contraindicated in pregnancy.

Glipizide was found to be mildly fetotoxic in rat reproductive studies. No teratogenic effects were found in rat or rabbit studies.

Prolonged severe hypoglycaemia (4 -10 days) has been reported in neonates born to mothers who were receiving a sulphonylurea drug at the time of delivery.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Breast feeding

No data are available on secretion into breast milk. Therefore glipizide is contraindicated in lactation.

4.7 Effects on ability to drive and use machines

The effect of glipizide on the ability to drive or operate machines has not been studied. However, there is no evidence to suggest that glipizide may affect these abilities. Patients should be aware of the symptoms of hypoglycaemia and be careful about driving and the use ofmachines, especially when optimum stabilisation has not been achieved, for example during the change-over from other medications or during irregular use.

4.8 Undesirable effects

The majority of side effects have been dose related, transient, and have responded to dose reduction or withdrawal of the medication. However, clinical experience thus far has shown that, as with other sulphonylureas, some side effects associated with hypersensitivity may be severe and deaths have been reported in some instances.

The reported adverse reactions, which may possibly be associated with glipizide, are listed in the following table by system organ class and frequency group: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to < 1/1000), Very rare (< 1/10,000), Not known (cannot be estimated from available data).

Blood and lymphatic system disorders:

Not known - Leukopenia, agranulocytosis, thrombocytopenia, haemolytic anaemia, pancytopenia

Metabolism and nutrition disorders:

Common – Hypoglycaemia

Not known – Hyponatraemia

Psychiatric disorders:

Not known – Confusional state[1]

Nervous system disorders:

Uncommon – Dizziness[1], somnolence[1], tremor[1]

Not known – Headache[1]

Eye disorders:

Uncommon – Vision blurred[1]

Not known – Diplopia[1], visual impairment[1], visual acuity reduced[1]

Gastrointestinal disorders:

Common – Nausea[2], diarrhoea[2], abdominal pain and upper[2] abdominal pain

Uncommon – Vomiting

Not known – Constipation[2]

Hepatobiliary disorders:

Uncommon – Jaundice cholestatic[3]

Not known – Hepatic function abnormal, hepatitis

Skin and subcutaneous tissue disorders:

Uncommon – Eczema[4]

Not known – Dermatitis allergic[4], erythema[4], rash morbilliform[4], rash maculopapular[4], urticaria[4], pruritus[4], photosensitivity reaction

Congenital, familial and genetic disorders:

Not known – Porphyria non-acute

General disorders and administration site conditions:

Not known – Malaise[1].

Investigations:

Not known – Aspartate aminotransferase increased[5], blood lactate dehydrogenase (BLT) increased[5], blood alkaline phosphatase increased[5], blood urea increased (BUN)[5], blood creatinine increased[5].

[1] They are This is usually transient and do not require discontinuance of therapy; however, they may also be symptoms of hypoglycaemia.

[2] Appear to be dose related and usually disappear on division or reduction of dosage.

[3] Discontinue treatment if cholestatic jaundice occurs.

[4] They frequently disappear with continued therapy. However, if they persist, the drug should be discontinued.

[5]The relationship of these abnormalities to glipizide is uncertain, and they have rarely been associated with clinical symptoms.

Aplastic anaemia and disulfiram-like reactions have been reported with other sulphonylureas.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form /https://sideeffects.health.gov.il

Additionally, you can also report to www.perrigo-pharma.co.il.

4.9 Overdose

There is no well documented experience with glipizide overdosage.

Overdosage of sulphonylureas including glipizide can produce glycaemia. Mild hypoglycaemic symptoms without loss of consciousness or neurologic findings should be treated actively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycaemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalisation. If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL (5.55 mmol/L). Patients should be closely monitored for a minimum of 48 hours and depending on the status of the patient at this time the physician should decide whether further monitoring is required. Clearance of glipizide from plasma may be prolonged in people with liver disease. Because of the extensive protein binding of glipizide, dialysis is unlikely to be of benefit.

## 5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, blood glucose lowering drugs excl. insulins, sulfonylureas, ATC code: A10BB07.

Glipizide is an oral blood glucose lowering drug of the sulphonylurea class. The primary mode of action of glipizide is the stimulation of insulin secretion from the beta-cells of pancreatic islet tissue. Stimulation of insulin secretion by glipizide in response to a meal is of major importance. Fasting insulin levels are not elevated even on long-term glipizide administration, but the post-prandial insulin response continues to be enhanced after at least 6 months of treatment. The insulinotropic response to a meal occurs within 30 minutes after oral dose of glipizide in diabetic patients, but elevated insulin levels do not persist beyond the time of the meal challenge. There is also increasing evidence that extrapancreatic effects involving potentiation of insulin action form a significant component of the activity of glipizide.

Blood sugar control persists for up to 24 hours after a single dose of glipizide, even though plasma levels have declined to a small fraction of peak levels by that time (see section 5.2).

## 5.2 Pharmacokinetic properties

### Absorption

Gastrointestinal absorption of glipizide in hummans is uniform, rapid and essentially complete. Peak plasma concentrations occur 1to 3 hours after a single oral dose. The half-life of elimination ranges from 2to 4 hours in normal subjects, whether given intravenously or orally. The metabolic and excretory patterns are similar with the two routes of administration, indicating that first-pass metabolism is not significant. Glipizide does not accumulate in plasma on repeated oral administration. Total absorption and disposition of an oral dose were unaffected by food in normal volunteers, but absorption was delayed by about 40 minutes. Thus, glipizide was more effective when administered about 30 minutes before, rather than with, a test meal in diabetic patients.

### Distribution

Protein binding was studied in serum from volunteers who received either oral or intravenous glipizide and found to be 98%to 99% one hour after either route of administration. The apparent volume of distribution of glipizide after intravenous administration was 11L, indicative of localisation within the extracellular fluid compartment. In mice, no glipizide or metabolites were detectable autoradiographically in the brain or spinal cord of males or females, nor in the foetuses of pregnant females. In another study, however, very small amounts of radioactivity were detected in the foetuses of rats given labelled drug.

### Biotransformation

The metabolism of glipizide is extensive and occurs mainly in the liver.

### Elimination

The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Less than 10% unchanged glipizide is found in urine.

## 5.3 Preclinical safety data

Acute toxicity studies showed no specific susceptibility. The acute oral toxicity of glipizide was extremely low in all species tested (LD50 greater than 4 g/kg). Chronic toxicity tests in rats and dogs at doses up to 8.0 mg/kg did not show any evidence of toxic effects.

A 20-month study in rats and an 18-month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug related carcinogenicity. Bacterial and in vivo mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the maximum human dose showed no effects on fertility.

**6. Pharmaceutical particulars**

6.1 List of excipients

Lactose 200, Microcrystalline cellulose, Maize starch, Stearic acid

6.2 Incompatibilities

None stated.

6.3 Shelf life

~~36 months.~~ The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store below $25^0$C.

6.5 Nature and contents of container

Blister strips containing 30 tablets

6.6 Special precautions for disposal and other handling

None.

7. Manufacturer and Registration authorisation holder

Perrigo Israel Pharmaceuticals, P.O.B 16, Yeruham Israel

8. Registration authorisation number

13227.27134

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