Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Glibenese 5 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains glipizide 5 mg

Excipients:
Anhydrous lactose 162.0 mg

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.
White, capsular-shaped, scored tablets, engraved Y2 on one side and bisected. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As an adjunct to diet, in Type 2 diabetes, where proper dietary management alone has failed.

4.2 Posology and method of administration

Route of administration: Oral.

As for any hypoglycaemic agent, dosage must be adapted for each individual patient.

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

In general, Glibenese should be given approximately 30 minutes before a meal to achieve the greatest reduction in post-prandial hyperglycaemia.

Initial Dose: The recommended starting dose is 5mg, given before breakfast or the midday meal. Elderly patients and other patients at risk for hypoglycaemia may be started on 2.5mg (see use in elderly and in high risk patients).

Titration: Dosage adjustments should ordinarily be in increments of 2.5 or 5mg, as determined by blood glucose response. At least several days should elapse between titration steps. The maximum recommended single dose is 15mg. Doses above 15mg should ordinarily be divided.

Maintenance: Some patients may be effectively controlled on a once-a-day regimen. Total daily dosage above 15mg should ordinarily be divided. Patients can usually be stabilised on a dosage ranging from 2.5 to 20mg daily. The maximum recommended daily dosage is 20mg.

Use in children: Safety and effectiveness in children have not been established.

Use in elderly and in high risk patients: To decrease the risk of hypoglycaemia in patients at risk including elderly patients, debilitated, malnourished or patients, with irregular caloric intake and patients with an impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycaemic reactions *(see Initial Dose and Section 4.4 special warning and precautions for use).*

Patients receiving insulin: As with other sulphonylurea class hypoglycaemics, many stable Type 2 diabetic patients receiving insulin may be transferred safely to treatment with glipizide. When transferring patients from insulin to Glibenese, the following general guidelines should be considered.

For patients whose daily insulin requirement is 20 units or less, insulin may be discontinued and Glibenese therapy begun at usual dosage. Several days should elapse between Glibenese titration steps.

For patients whose daily insulin requirement is greater than 20 units, the insulin dose should be reduced by 50% and Glibenese therapy initiated at usual dosages. Subsequent reductions in insulin dosage should depend on individual patient response. Several days should elapse between Glibenese titration steps.

During the insulin withdrawal period, the patient should self-monitor glucose levels. Patients should be instructed to contact the prescriber immediately if these tests are abnormal.

In some cases, especially when the patient has been receiving greater than 40 units of insulin daily, it may be advisable to consider hospitalisation during the transition period.

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

Combination Use: when adding other blood-glucose-lowering agents to glipizide for combination therapy, the agent should be initiated at the lowest recommended dose and patients should be observed carefully for hypoglycaemia. Refer to the product information supplied with the oral agent for additional information.

When adding glipizide to other blood-glucose lowering agents, glipizide can be initiated at 5mg. Those patients who may be more sensitive to hypoglycaemia drugs may be started at a lower dose. Titration should be based on clinical judgement.

4.3 Contraindications

Glipizide is contra-indicated in the following conditions:

1. Patients who are hypersensitive to glipizide or any excipients in the tablets.
2. Type I (or Juvenile-onset) diabetes.
3. Severe or unstable ‘brittle’ diabetes.
4. Diabetic ketoacidosis, diabetic coma or diabetes complicated by major surgery, severe sepsis or severe trauma.
5. Severe renal, hepatic or thyroid impairment; coexistent renal and hepatic disease.

4.4 Special warnings and precautions for use

Hypoglycaemia: All sulphonylurea drugs including glipizide are capable of producing severe hypoglycaemia which may result in coma, and may require hospitalisation. Patients experiencing severe hypoglycaemia should be managed with appropriate glucose therapy and be monitored for a minimum of 24 to 48 hours.

Proper patient selection, dosage, and instructions are important to avoid hypoglycaemic episodes. Regular, timely carbohydrate intake is important to avoid hypoglycaemia events occurring when a meal is delayed or insufficient food is eaten or carbohydrate intake is unbalanced.

Renal or hepatic insufficiency may affect the disposition 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. 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 any 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 the diabetes or 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.

Laboratory tests: Blood glucose should be monitored periodically. Measurements of glycosylated haemoglobin should be performed and goals assessed by the current standard of care.

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:
The risk 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 failures should also be explained. Patients should be informed of the potential risks and advantages of Glibenese and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise programme and of regular testing of blood glucose.

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

4.5 Interaction with other medicinal products and other forms of interaction

The following products are likely to increase the hypoglycaemia effect:

Miconazole: Increase in hypoglycaemic effects, possibly leading to symptoms of hypoglycaemia or even coma.

Fluconazole: There have been reports of hypoglycaemia following the co-administration of glipizide and fluconazole, possibly the result of an increased half-life of glipizide.

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.

Nonsteroidal anti-inflammatory agents (NSAIDS): (e.g. phenylbutazone) Increase in hypoglycaemia effect of sulphonylureas (displacement of sulphonylurea binding to plasma proteins and/or decrease in sulphonylurea elimination).

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

Alcohol: Increase in hypoglycaemic reaction which can lead to hypoglycaemic coma.

Beta-blockers: All beta-blockers mask some of the symptoms of hypoglycaemia, e.g., palpitations and tachycardia. Most non-cardioselective 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, including glipizide. Therefore, a reduction in glipizide dosage may be required.

H_2 receptor Antagonists: The use of H_2 receptor antagonists (ie. cimetidine) may potentiate the hypoglycaemic effects of sulphonylureas, including glipizide.

The hypoglycaemic action of sulphonylurea in general may also be potentiated by monoamine oxidase inhibitors and drugs that are highly protein bound, such as sulphonamides, chloramphenicol, probenecid and coumarins. 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).
In vitro binding studies with human serum proteins indicate that glipizide binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to the clinical situation in the use of glipizide with these drugs.

The following products could lead to hyperglycaemia:

Phenothiazines: (e.g. chlorpromazine) at high dose (> 100mg per 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.

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

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

4.6 Pregnancy and lactation

Use in pregnancy: Glipizide is contra-indicated during pregnancy. Serious consideration should be given to the potential hazard of using glipizide in women of childbearing age who may become pregnant.

Nursing mothers: Although it is not known whether glipizide is excreted in human milk, some sulphonylurea drugs are known to be so. It is therefore not recommended that a woman breast feed while taking this medication.

4.7 Effects on ability to drive and use machines

The effect of glipizide on the ability to drive or operate machinery has not been studied, however, there is no evidence to suggest that glipizide may effect these abilities. Patients should be aware of the symptoms of hypoglycaemia and be careful about driving and the use of machinery.

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.

Side effects listed in this section marked with * are usually transient and so do not require discontinuance of therapy; however, they may also be symptoms of hypoglycaemia.

Blood and Lymphatic System Disorders: Agranulocytosis, leucopenia, thrombocytopenia, haemolytic anaemia and pancytopenia have been reported. Aplastic anaemia has been reported with other sulphonylureas.

Metabolism and Nutrition Disorders: Hypoglycaemia *(see section 4.4 special Warning and Precautions for Use and section 4.9 Overdose).* Hyponatraemia has been reported. Disulfiram-like reactions have been reported with other sulfonylureas.

Psychiatric Disorder: Confusion*

Nervous System Disorder: dizziness*, drowsiness*, headache* and tremor*, have been reported in patients treated with glipizide.

Eye Disorder: visual disturbance such as blurred vision*, diplopia* and abnormal vision* including visual impairment* and decreased vision*, have been reported in patients treated with glipizide.

Gastrointestinal Disorders: nausea, diarrhoea, constipation and gastralgia. They appear to be dose related and usually disappear on division or reduction of dosage. Abnormal pain and vomiting.

Hepatobiliary Disorders: cholestatic jaundice, impaired hepatic function and hepatitis have been reported. Discontinue treatment if cholestatic jaundice occurs. Hepatic porphyria and porphyria cutanea tarda have been reported.

Skin and Subcutaneous Tissue Disorders: allergic skin reactions including erythema, morbilliform or maculopapular reactions, urticaria, pruritus and eczema have been reported. They frequently disappear with continued therapy. However, if they persist, the drug should be discontinued. As with other sulphonylureas, photosensitivity reaction have been reported.

General Disorder and Administration Site Conditions: Malaise*

Laboratory Investigations: Occasional mild to moderate elevations of AST (SGOT), LDH, alkaline phosphatase, BUN and creatinine were noted. The relationship of these abnormalities to glipizide is uncertain and they have rarely been associated with clinical symptoms.

4.9 Overdose

There is no well documented experience with glipizide overdosage. The acute oral toxicity was extremely low in all species tested (LD_{50} greater than 4g/kg).

Overdosage of sulphonylureas including glipizide can produce hypoglycaemia. Mild hypoglycaemic symptoms without loss of consciousness or neurological findings should be treated aggressively 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 continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 5.6mmol/1 (100mg/dl).

Patients should be closely monitored for a minimum of 24 to 48 hours and depending on the status of the patient at this time the physician should decided whether further monitoring is required. Clearance of glipizide from plasma may be prolonged in persons 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

Glipizide is an orally active sulphonylurea which effectively reduces blood glucose to the normal range in properly selected patients with non-insulin-dependent diabetes mellitus (NIDDM). It eliminates or diminishes glycosuria and ameliorates symptoms such as polyuria, polydipsia and pruritus.

The primary mode of action of glipizide in experimental animals is the stimulation of insulin secretion from the beta-cells of pancreatic islet tissue. In man, stimulation of insulin secretion by glipizide in response to a meal is undoubtedly 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 an 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. Once-daily administration of doses up to 15mg has been shown to be safe and effective maintenance therapy in selected patients.

Some patients fail to respond initially, or gradually lose their responsiveness to sulphonylurea drugs, including glipizide. Alternatively, glipizide, may be effective in some patients who have not responded or have ceased to respond to other sulphonylureas.

5.2 Pharmacokinetic properties

Gastrointestinal absorption of glipizide in man is uniform, rapid and essentially complete. Peak plasma concentrations occur 1-3 hours after a single oral dose.

The half-life of elimination ranges from 2-4 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 was 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. Protein binding was studied in serum from volunteers who received either oral or intravenous glipizide and found to be 98%-99% one hour after either route of administration. The apparent volume of distribution of glipizide after intravenous administration was 11 litres, indicative of localisation within the extracellular fluid compartment.

The metabolism of glipizide is extensive and occurs mainly in the liver. 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 the urine.
In a placebo-controlled crossover study in normal volunteers, glipizide showed no anti-diuretic activity, and in fact led to a slight increase in free water clearance.

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 (LD_{50} greater than 4g/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 human dose showed no effects on fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous lactose
Maize starch
Microcrystalline cellulose
Stearic acid 50

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

Glibenese Tablets are supplied in packs of 56 tablets. The blister is formed from 250µm white opaque PVC coated with 40gm^2 PVdC and backed with 20µm hard tempered aluminium foil, coated with 7gm^2 of sealing lacquer.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
UK

8 MARKETING AUTHORISATION NUMBER

PA 0019/002/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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