SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gliclazide 40 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 40 mg gliclazide.

Excipient(s) with known effect: Each tablet contains 67.120 mg of lactose (as lactose monohydrate).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White, oval, biconvex tablets debossed with G40 on one side and plain on other side with approximate length 8.50 mm and width 4.50 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non insulin dependent diabetes (type 2) in adults when dietary measures, physical exercise and weight loss alone are not sufficient to control blood glucose.

4.2 Posology and method of administration

Posology

- Initial dose

The total daily dose may vary from 40 to 320 mg taken orally. The dose should be adjusted according to the individual patient's response, commencing with 40-80 mg (1-2 tablets) daily and increasing until adequate control is achieved. A single dose should not exceed 160 mg. When higher doses are

required, Gliclazide 40 mg tablets should be taken 4 times daily and according to the main meals of the day.

In obese patients or those not showing adequate response to Gliclazide 40 mg tablets alone, additional therapy may be required.

- Switching from another oral antidiabetic agent to Gliclazide 40 mg:

Gliclazide 40 mg can be used to replace other oral antidiabetic agents.

The dosage and the half-life of the previous antidiabetic agent should be taken into account when switching to Gliclazide 40 mg tablets.

A transitional period is not generally necessary. A starting dose of 40-80 mg (1-2 tablets) should be used and this should be adjusted to suit patient's blood glucose response, as described above.

When switching from a hypoglycaemic sulfonylurea with prolonged half-life, a treatment free period of a few days may be necessary to avoid an additive effect of the two products, which might cause hypoglycaemia.

- Combination treatment with other antidiabetic agents:

Gliclazide 40 mg tablets can be given in combination with biguanides, alpha glucosidase inhibitors or insulin.

In patients not adequately controlled with Gliclazide 40 mg, concomitant insulin therapy can be initiated under close medical supervision.

Special Populations

Elderly

Gliclazide 40 mg tablets should be prescribed using the same dosing regimen recommended for patients under 65 years of age.

Renal Impairment

In patients with mild to moderate renal insufficiency, the same dosing regimen can be used as in patients with normal renal function with careful patient monitoring. These data have been confirmed in clinical trials.

Patients at risk of hypoglycaemia

- Undernourished or malnourished,
- Severe or poorly compensated endocrine disorders (hypopituitarism, hypothyroidism, adrenocorticotrophic insufficiency),
- Withdrawal of prolonged and/ or high dose corticosteroid therapy,
- Severe vascular disease (severe coronary heart disease, severe carotid impairment, diffuse vascular disease).

It is recommended that the minimum daily starting dose of 40-80 mg is used.

Paediatric population

The safety and efficacy of Gliclazide 40 mg tablets in children and adolescents have not been established. No data are available.

Route of Administration

Oral administration.

4.3 Contraindications

This medicine is contra-indicated in case of:

- Hypersensitivity to Gliclazide or to any of the excipients listed in section 6.1, other sulfonylureas, sulphonamides,
- Type 1 diabetes,
- Diabetic pre-coma and coma, diabetic keto-acidosis,
- Severe renal or hepatic insufficiency: in these cases the use of insulin is recommended,
- Treatment with miconazole (see section 4.5),
- Lactation (see section 4.6).

4.4 Special warnings and precautions for use

Hypoglycaemia:

This treatment should be prescribed only if the patient is likely to have a regular food intake (including breakfast). It is important to have a regular carbohydrate intake due to the increased risk of hypoglycaemia if a meal is taken late, if an inadequate amount of food is consumed or if the food is low in carbohydrate. Hypoglycaemia is more likely to occur during low-calorie diets, following prolonged or strenuous exercise, alcohol intake or if a combination of hypoglycaemic agents is being used.

Hypoglycaemia may occur following administration of sulfonylureas (see section 4.8). Some cases may be severe and prolonged. Hospitalization may be necessary and glucose administration may need to be continued for several days.

Careful selection of patients, of the dose used, and clear patient directions are necessary to reduce the risk of hypoglycaemic episodes.

Factors which increase the risk of hypoglycaemia:

- patient refuses or (particularly in elderly subjects) is unable to co-operate,
- malnutrition, irregular mealtimes, skipping meals, periods of fasting or dietary changes,
- imbalance between physical exercise and carbohydrate intake,
- renal insufficiency,
- severe hepatic insufficiency,
- overdose of Gliclazide 40 mg Tablets,
- certain endocrine disorders, thyroid disorders, hypopituitarism and adrenal insufficiency,
- concomitant administration of certain other medicines (see section 4.5).

Renal and hepatic insufficiency: the pharmacokinetics and/or pharmacodynamics of gliclazide may be altered in patients with hepatic insufficiency or severe renal failure. A hypoglycaemic episode occurring in

these patients may be prolonged, so appropriate management should be initiated.

Patient information: the risks of hypoglycaemia, together with its symptoms (see section 4.8), treatment, and conditions that predispose to its development, should be explained to the patient and to the family members.

The patients should be informed of the importance of following dietary advice, of taking regular exercise, and of regular monitoring of blood glucose levels.

Poor blood glucose control: blood glucose control in patient receiving antidiabetic treatment may be affected by any of the following: St. John's Wort (*Hypericum perforatum*) preparations (see section 4.5), fever, trauma, infection or surgical intervention. In some cases, it may be necessary to administer insulin.

The hypoglycaemic efficacy of any oral antidiabetic agent, including Gliclazide, is attenuated over time in many patients: this may be due to progression in the severity of the diabetes, or to a reduced response to treatment. This phenomenon is known as secondary failure which is distinct from primary failure, when an active substance is ineffective as first-line treatment. Adequate dose adjustment and dietary compliance should be considered before classifying the patient as secondary failure.

Dysglycaemia:

Disturbances in blood glucose, including hypoglycaemia and hyperglycaemia have been reported, in diabetic patients receiving concomitant treatment with fluoroquinolones, especially in elderly patients. Indeed, careful monitoring of blood glucose is recommended in all patients receiving at the same time Gliclazide 40 mg and a fluoroquinolone.

Laboratory tests: Measurement of glycated haemoglobin levels (or fasting venous plasma glucose) is recommended in assessing blood glucose control. Blood glucose self-monitoring may also be useful.

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

Porphyric patients:

Cases of acute porphyria have been described with some other sulfonylurea drugs, in patients who have porphyria.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or 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 risk of hypoglycaemia

Contra-indicated combination

- **Miconazole** (systemic route, oromucosal gel): increases the hypoglycaemic effect with possible onset of hypoglycaemic symptoms, or even coma.

Combinations which are not recommended

- **Phenylbutazone** (systemic route): increases the hypoglycaemic effect of sulfonylureas (displaces their binding to plasma proteins and/or reduces their elimination).

It is preferable to use a different anti-inflammatory agent, or else to warn the patient and emphasise the importance of self-monitoring. Where necessary, adjust the dose during and after treatment with the anti-inflammatory agent.

- **Alcohol**: increases the hypoglycaemic reaction (by inhibiting compensatory reactions) that can lead to the onset of hypoglycaemic coma.

Avoid alcohol or medicines containing alcohol.

Combinations requiring precautions for use

Potentiation of blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur when one of the following drugs is taken:

Other antidiabetic agents (insulins, acarbose, metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists), beta-blockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H2-receptor antagonists, MAOIs, sulfonamides, clarithromycin and nonsteroidal anti-inflammatory agents.

The following products may cause an increase in blood glucose levels

Combination which is not recommended

- **Danazol**: diabetogenic effect of danazol.

If the use of this active substance cannot be avoided, warn the patient and emphasise the importance of urine and blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic agent during and after treatment with danazol.

Combination requiring precautions during use

- **Chlorpromazine** (neuroleptic agent): high doses (> 100 mg per day of chlorpromazine) increase blood glucose levels (reduced insulin release).

Warn the patient and emphasize the importance of blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic active substance during and after treatment with the neuroleptic agent.

- **Glucocorticoids** (systemic and local route: intra-articular, cutaneous and rectal preparations) and tetracosactrin: increase in blood glucose levels with possible ketosis (reduced tolerance to carbohydrates due to glucocorticoids).

Warn the patient and emphasize the importance of blood glucose monitoring, particularly at the start of the treatment. It may be necessary to adjust the dose of the antidiabetic active substance during and after treatment with glucocorticoids.

- **Ritodrine, salbutamol, terbutaline:** (I.V)

Increased blood glucose levels due to beta-2 agonist effects.

Emphasise the importance of monitoring blood glucose levels. If necessary, switch to insulin.

- **Saint John's Wort (Hypericum perforatum) preparations:**

Gliclazide exposure is decreased by St John's Wort-*Hypericum perforatum*. Emphasise the importance of blood glucose levels monitoring.

The following products may cause Dysglycaemia

Combinations requiring precautions during use

- **Fluoroquinolones**: in case of a concomitant use of Gliclazide and a fluoroquinolone, the patient should be warned of the risk of dysglycaemia, and the importance of blood glucose monitoring should be emphasised.

Combination which must be taken into account

- **Anticoagulant therapy (warfarin):**

Sulfonylureas may lead to potentiation of anticoagulation during concurrent treatment.

Adjustment of anticoagulant may be necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There is no or limited amount of data (less than 300 pregnancy outcomes) from the use of gliclazide in pregnant women, even though there are few data with other sulfonylureas.

In animal studies, gliclazide is not teratogenic (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of gliclazide during pregnancy.

Control of diabetes should be obtained before the time of conception to reduce the risk of congenital abnormalities linked to uncontrolled diabetes.

Oral hypoglycaemic agents are not suitable, insulin is the drug of first choice for treatment of diabetes during pregnancy. It is recommended that oral hypoglycaemic therapy is changed to insulin before a pregnancy is attempted, or as soon as pregnancy is discovered.

Breast-feeding:

It is unknown whether gliclazide or its metabolites are excreted in human milk. Given the risk of neonatal hypoglycaemia, the product is therefore contra-indicated in breast-feeding mothers. A risk to the newborns/infants cannot be excluded.

Fertility:

No effect on fertility or reproductive performance was noted in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Gliclazide 40 mg has no or negligible influence on the ability to drive and use machines. However, patients should be informed that their concentration may be affected if their diabetes is not satisfactorily controlled, especially at the beginning of treatment (see section 4.4).

4.8 Undesirable effects

Based on the experience with gliclazide, the following undesirable effects have been reported.

The most frequent adverse reaction with gliclazide is hypoglycaemia.

As for other sulfonylureas, treatment with Gliclazide 40 mg Tablets can cause hypoglycaemia, if mealtimes are irregular and, in particular, if meals are skipped. Possible symptoms of hypoglycaemia are: headache, intense hunger, nausea, vomiting, lassitude, sleep disorders, agitation, aggression, poor concentration, reduced awareness and slowed reactions, depression, confusion, visual and speech disorders, aphasia, tremor, paresis, sensory disorders, dizziness, feeling of powerlessness, loss of self-control, delirium, convulsions, shallow respiration, bradycardia, drowsiness and loss of consciousness, possibly resulting in coma and lethal outcome.

In addition, signs of adrenergic counter-regulation may be observed: sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmia.

Usually, symptoms disappear after intake of carbohydrates (sugar). However artificial sweeteners have no effect. Experience with other sulfonylureas shows that hypoglycaemia can recur even when measures prove effective initially.

If a hypoglycaemic episode is severe or prolonged, and even if it is temporarily controlled by intake of sugar, immediate medical treatment or even hospitalisation are required.

Gastrointestinal disturbances, including abdominal pain, nausea, vomiting dyspepsia, diarrhoea, and constipation have been reported: if these should occur they can be avoided or minimised if gliclazide is taken with breakfast.

The following undesirable effects have been more rarely reported:

- Skin and subcutaneous tissue disorders: rash, pruritus, urticaria, angioedema, erythema, maculopapular rashes, bullous reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis and autoimmune bullous disorders), and exceptionally, drug rash with eosinophilia and systemic symptoms (DRESS).
- Blood and lymphatic system disorders: changes in haematology are rare. They may include anaemia, leucopenia, thrombocytopenia,

granulocytopenia. These are in general reversible upon discontinuation of medication.

- Hepato-biliary disorders: raised hepatic enzyme levels (AST, ALT, alkaline phosphatase), hepatitis (isolated reports). Discontinue treatment if cholestatic jaundice appears. These symptoms usually disappear after discontinuation of treatment.
- Eye disorders: transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.
- Class attribution effects:
  As for other sulfonylureas, the following adverse events have been observed: cases of erthrocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia, allergic vasculitis, hyponatremia, elevated liver enzyme levels and even impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis which regressed after withdrawal of the sulfonylurea or led to life-threatening liver failure in isolated cases.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

An overdose of sulfonylureas may cause hypoglycaemia.

Moderate symptoms of hypoglycaemia, without any loss of consciousness or neurological signs, must be corrected by carbohydrate intake, dose adjustment and/or change of diet. Strict monitoring should be continued until the doctor is sure that the patient is out of danger.

Severe hypoglycaemic reactions, with coma, convulsions or other neurological disorders are possible and must be treated as a medical emergency, requiring immediate hospitalisation.

If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid I.V. injection of 50 mL of concentrated glucose solution (20 to 30 %). This should be followed by continuous infusion of a more dilute glucose solution (10 %) at a rate that will maintain blood glucose levels above 1 g/L. Patients should be monitored closely and, depending on the patient's condition after this time, the doctor will decide if further monitoring is necessary.

Dialysis is of no benefit to patients due to the strong binding of gliclazide to proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sulfonamides, urea derivatives. ATC code: A10BB09.

Mechanism of Action

Gliclazide is a hypoglycaemic sulfonylurea antidiabetic active substance differing from other related compounds by an N-containing heterocyclic ring with an endocyclic bond.

Gliclazide reduces blood glucose levels by stimulating insulin secretion from the β- cells of the islets of Langerhans. Increase in postprandial insulin and C-peptide secretion persists after two years of treatment.

In addition to these metabolic properties, gliclazide has haemovascular properties.

Clinical efficacy and safety

Effects on insulin release:

In type 2 diabetics, gliclazide restores the first peak of insulin secretion in response to glucose and increases the second phase of insulin secretion. A significant increase in insulin response is seen in response to stimulation induced by a meal or glucose.

Haemovascular properties:

Gliclazide decreases microthrombosis by two mechanisms which may be involved in complications of diabetes:

- A partial inhibition of platelet aggregation and adhesion, with a decrease in the markers of platelet activation (beta thromboglobulin, thromboxane B2).
- An action on the vascular endothelium fibrinolytic activity with an increase in tPA activity.

5.2 Pharmacokinetic properties

Absorption

Plasma levels increase reaching maximal concentrations between 2 and 6 hours. Gliclazide is well absorbed. Food intake does not affect the rate or degree of absorption.

Distribution

Plasma protein binding is approximately 95%. The volume of distribution is around 19 litres.

Biotransformation

Gliclazide is mainly metabolised in the liver and excreted in urine; less than 1% of the dose is excreted unchanged in the urine. No active metabolites have been detected in plasma.

Elimination

The elimination half-life of gliclazide is between 10 and 12 hours.

Linearity/ non-linearity

The relationship between the dose administered between 40 to 400 mg and the mean plasma concentrations is linear.

Special populations

Elderly

No clinically significant changes in the pharmacokinetic parameters have been observed in elderly patients.

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of repeated dose toxicity and genotoxicity. Long term carcinogenicity studies have not been done. No teratogenic changes have been shown in animal studies, but lower foetal body weight was observed in animals receiving doses 9.4 fold higher than the maximum recommended dose in humans. Fertility and reproductive performance were unaffected after gliclazide administration in animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate

Povidone K 25

Maize Starch

Talc

Magnesium Stearate

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Plain Aluminium blister foil with clear PVC film.
Pack sizes: 7, 14, 20, 28, 56, 60, 84 and 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Brown & Burk UK Ltd
5, Marryat Close
Hounslow West
Middlesex
TW4 5DQ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 25298/0253

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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