

PRODUCT MONOGRAPH

^{Pr}GLICLAZIDE MR

Gliclazide Modified Release Tablets

30 mg

Hypoglycemic sulfonylurea - Oral antidiabetic agent

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**Date of Preparation:
June 25, 2010**

Control No: 139545

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^{Pr}**GLICLAZIDE MR**
Gliclazide Modified Release Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|--------------------------------|-------------------------------|--|
| Oral | 30 mg | <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i> |

INDICATIONS AND CLINICAL USE

GLICLAZIDE MR is indicated for:

Control of hyperglycemia in gliclazide responsive diabetes mellitus of stable, mild, non-ketosis prone, maturity onset or adult type which cannot be controlled by proper dietary management and exercise, or when insulin therapy is not appropriate.

Geriatrics (≥ 65 years of age):

The efficacy and tolerance of GLICLAZIDE MR, prescribed using the same therapeutic regimen in subjects over 65 years, has been confirmed in clinical trials. The dosage will therefore be identical to that recommended for adults under the age of 65 years.

Pediatrics (< 18 years of age):

Safety and effectiveness of GLICLAZIDE MR in children have not been established. GLICLAZIDE MR is therefore not recommended for use in children and adolescents.

CONTRAINDICATIONS

GLICLAZIDE MR is contraindicated in patients with:

- Known hypersensitivity or allergy to gliclazide, other sulfonylureas, sulfonamides, or to any of the excipients of this product. (For a complete listing see DOSAGE FORMS,

COMPOSITION AND PACKAGING SECTION).

- Unstable and/or insulin-dependent diabetes mellitus, particularly juvenile diabetes, diabetic ketoacidosis, diabetic pre-coma and coma.
- During stress conditions such as serious infection, trauma or surgery. In the presence of severe liver disease or renal impairment (see WARNINGS AND PRECAUTIONS)
- Treatment with miconazole via systemic route or oromucosal gel (see DRUG-DRUG INTERACTIONS).
- Pregnancy and lactation (see WARNINGS AND PRECAUTIONS, Special Population, Pregnant Women and Nursing Women).

WARNINGS AND PRECAUTIONS

General

Use of GLICLAZIDE MR (gliclazide) must be considered as treatment in addition to proper dietary regimen and not as substitute for diet.

Careful selection of patients is important. It is imperative that there be rigid attention to diet, careful adjustment of dosage and instruction of the patient on hypoglycemic reactions, their recognition, remedies and control as well as regular, thorough medical follow-up.

Since the effects of oral hypoglycemic agents on the vascular changes and other long-term sequelae of diabetes mellitus are not fully known, patients receiving such drugs must be closely observed for both short- and long-term complications. Periodic assessment of cardiovascular, ophthalmic, renal and hepatic status is advisable.

GLICLAZIDE MR use is not recommended with medications containing alcohol, phenylbutazone (systemic route) and danazol and precautions are required when used with chlorpromazine, glucocorticoids, ritodrine, salbutamol, terbutaline and anticoagulant therapy (see DRUG-DRUG INTERACTIONS).

Carcinogenesis and Mutagenesis

See Toxicology

Endocrine and Metabolism

Hypoglycemic reactions

As with other sulfonylurea drugs, manifestations of hypoglycemia including dizziness, lack of energy, drowsiness, headache and sweating have been observed and weakness, nervousness, shakiness and paresthesia have also been reported. All sulfonylurea drugs can induce severe hypoglycemia. Particularly susceptible are elderly subjects, patients with impaired hepatic or renal function, those who are debilitated or malnourished and patients with primary or secondary adrenal insufficiency. Some cases may be severe and prolonged. Hospitalisation may be necessary and glucose administration may need to be continued for several days. Hypoglycemia may be difficult to recognize in elderly patients and in patients receiving beta-blockers.

Possible other symptoms of hypoglycemia are: 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, 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: clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmia.

This treatment should only be prescribed 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 hypoglycemia if a meal is taken late, if an inadequate amount of food is consumed or if the food is low in carbohydrate. Hypoglycemia is more likely to occur during periods of low-calorie diet, following prolonged or strenuous exercise, following alcohol intake or during the administration of a combination of hypoglycemic agents.

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

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

Other factors which increase the risk of hypoglycemia are: overdose of GLICLAZIDE MR, certain endocrine disorders (thyroid disorders, hypopituitarism and adrenal insufficiency) as well as withdrawal of prolonged and/or high dose corticosteroid therapy, severe vascular disease (severe coronary heart disease, severe carotid impairment, diffuse vascular disease) and concomitant administration of certain medicines (See DRUG-DRUG INTERACTIONS).

Poor Blood Glucose Control:

The efficacy of gliclazide, in reducing glucose to the desired level decreases over a long period of 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 and should be distinguished from primary failure, when the drug is ineffective when prescribed as first-line treatment. Adequate dose adjustment and compliance with dietary measures should be considered before classifying the patient as secondary failure. If a loss of adequate blood glucose-lowering response to GLICLAZIDE MR is detected, the drug should be discontinued.

Hepatic

The metabolism and excretion of sulfonylureas including GLICLAZIDE MR, may be slowed in patients with impaired hepatic function. (See Monitoring and Laboratory Tests).

Peri-Operative Considerations

In patients stabilized on gliclazide therapy, loss of blood sugar control may occur in cases of acute intercurrent disease or in stressful situations such as trauma or surgery. Under these conditions, discontinuation of GLICLAZIDE MR (gliclazide) and administration of insulin should be considered.

Renal

The metabolism and excretion of sulfonylureas including GLICLAZIDE MR, may be slowed in patients with impaired renal function. If hypoglycemia should occur in such patients, it may be

prolonged and appropriate management should be instituted (See Monitoring and Laboratory Tests).

Special Populations

Pregnant Women:

Gliclazide is contraindicated in pregnancy. It is recommended that insulin be used during pregnancy in diabetic women (See CONTRAINDICATIONS).

Uncontrolled diabetes (gestational or not) is associated with a higher incidence of congenital abnormalities and perinatal mortality. Blood glucose control should be optimal around the time of conception to reduce the risk of congenital malformations.

Nursing Women:

The product is contraindicated in breast-feeding mothers because the potential for hypoglycemia in nursing infants may exist. Some sulfonylurea drugs are excreted in human milk although it is not known whether gliclazide is one of them (See CONTRAINDICATIONS).

Pediatrics (< 18 years of age):

Safety and effectiveness of GLICLAZIDE MR in children have not been established. GLICLAZIDE MR is therefore not recommended for use in children and adolescents.

Geriatrics (\geq 65 years of age):

Efficacy and tolerance of GLICLAZIDE MR, prescribed using the same therapeutic regimen in subjects over 65 years, has been confirmed in clinical trials. Severe hypoglycemia can be induced by all sulfonylurea drugs, particularly susceptible are elderly subjects.

Monitoring and Laboratory Tests

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

recommended. Blood glucose control in a patient receiving antidiabetic treatment may be affected by fever and infection or surgical intervention. Closed monitoring is required in these patients. In some cases, it may be necessary to administer insulin.

Hepatic function should be assessed before initiating therapy and the liver function should be assessed periodically in patients with impaired hepatic function. In patients with impaired renal function, blood and urine glucose should be regularly monitored. Measurements of glycosylated hemoglobin levels are recommended.

Elderly patients (malnourished, with impaired hepatic, renal, or adrenal function) will require periodic monitoring and special care.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Gliclazide modified release tablets 30 mg have been evaluated for safety in controlled clinical trials in 955 patients, of which 728 were treated in long-term studies for up to 10 months, in comparison with gliclazide 80 mg tablets.

The percentage of patients discontinuing treatment due to adverse events was lower in the gliclazide modified release tablets 30 mg group (2.9%) than in the gliclazide 80 mg tablets group (4.5%).

The most frequently reported serious adverse events during clinical trials were coronary heart disease, cerebrovascular accidents, carcinoma, and gastrointestinal events (diarrhea, constipation, nausea, vomiting, gastritis, flatulence, dyspepsia).

The most frequent adverse event is hypoglycemia.

Serious adverse drug reactions that resulted in hospitalization during clinical trials were malaise, acute renal failure, and thrombophlebitis.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Hypoglycemia (See WARNINGS AND PRECAUTIONS)

Severe hypoglycemia which mimics acute CNS disorders may occur. Hepatic and/or renal disease, malnutrition, debility, advanced age, alcoholism, adrenal or pituitary insufficiency may be predisposing factors.

In long-term studies, the percentage of patients experiencing hypoglycemic episodes was similar between patients treated with gliclazide modified release tablets 30 mg (11.6%) and those treated with gliclazide 80 mg tablets (11.1%). However, the number of hypoglycemic episodes for 100 patient-months was lower in the gliclazide modified release tablets 30 mg group (3.5) than in the gliclazide 80 mg tablets group (4.8).

Analysis in elderly patients (over 65 years old) showed that this population experienced, overall, less hypoglycemia than the whole population with a prevalence of hypoglycemic episodes lower in the gliclazide modified release tablets 30 mg group (2.6 hypoglycemic episodes for 100 patient-months) than in the gliclazide 80 mg tablets group (4.1).

Other adverse events

Adverse events reported during controlled clinical trials with gliclazide modified release tablets 30 mg were those expected in the population of interest, a population whose underlying disease is recognized atheromatous risk factor.

Adverse events that have been reported in at least 1.0% of diabetic patients in long-term controlled studies, whatever their relationship to treatment, are listed by body system in the following table. The most frequent adverse events were unspecific of the disease as respiratory infections or back pain.

| | Gliclazide Modified Release Tablets 30 mg (n= 728) % | Gliclazide 80 mg tablets (n= 734) % |
|-----------------------------|---|--|
| Resistance mechanism | | |
| Infection viral | 7.7 | 5.6 |
| Otitis media | 1.1 | 0.8 |
| Respiratory | | |
| Rhinitis | 4.4 | 4.6 |
| Bronchitis | 4.4 | 4.6 |
| Pharyngitis | 4.3 | 3.5 |
| Upper respiratory infection | 3.3 | 3.7 |
| Coughing | 2.1 | 2.0 |
| Pneumonia | 1.5 | 1.4 |
| Sinusitis | 1.5 | 1.1 |
| Musculo-skeletal | | |
| Back pain | 5.2 | 4.1 |
| Arthralgia | 3.0 | 3.5 |
| Arthrosis | 2.2 | 2.2 |
| Arthritis | 1.4 | 2.3 |
| Tendinitis | 1.1 | 1.0 |
| Myalgia | 2.3 | 1.5 |
| Secondary term | | |
| Inflicted injury | 4.3 | 4.5 |
| Body as a whole | | |
| Headache | 3.8 | 4.6 |
| Asthenia | 2.2 | 2.6 |
| Cardiovascular | | |

| | | |
|--|-----|-----|
| Hypertension | 3.2 | 3.7 |
| Angina pectoris | 2.1 | 2.2 |
| Oedema legs | 1.2 | 1.4 |
| Urinary | | |
| Urinary tract infections | 2.6 | 3.0 |
| Gastrointestinal | | |
| Diarrhea | 2.5 | 2.0 |
| Constipation | 1.6 | 1.2 |
| Gastritis | 1.2 | 0.5 |
| Gastroenteritis | 1.1 | 1.5 |
| Nausea | 1.1 | 0.7 |
| Abdominal pain | 1.1 | 1.4 |
| Central, periph. nervous system | | |
| Dizziness | 2.2 | 2.3 |
| Neuralgia | 1.2 | 0.7 |
| Metabolism and nutrition | | |
| Hyperglycemia | 1.9 | 2.2 |
| Lipid metabolism disorder | 1.4 | 0.5 |
| Hyperlipaemia | 1.0 | 0.8 |
| Skin and appendages disorders | | |
| Dermatitis | 1.6 | 1.2 |
| Rash | 1.0 | 1.2 |
| Skin disorder | 1.9 | 2.0 |
| Pruritus | 1.0 | 0.4 |
| Vision disorders | | |

| | | |
|------------------------------|-----|-----|
| Conjunctivitis | 1.0 | 0.8 |
| Psychiatric disorders | | |
| Depression | 1.9 | 1.2 |
| Insomnia | 1.1 | 2.0 |

Analysis of adverse events in sub-populations led to similar patterns as in the whole population and showed that sex, age and renal insufficiency had no significant influence on the safety profile of 30 mg.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Adverse events other than those already specifically mentioned in this product monograph and that have been reported with gliclazide modified release tablets 30 mg during long-term studies in more than one patient and/or that have been previously reported with gliclazide 80 mg tablets or with other sulfonylurea drugs include the following (drug relationship has not been proved for all cases):

Body as a whole: allergy, carpal tunnel syndrome, chest pain, fever, infection, fungal infection, leg pain, malaise, pain, weight increase.

Cardiovascular: arteritis, cardiac failure, cerebrovascular disorder, coronary artery disorder, epistaxis, hypotension, myocardial infarction, palpitation, tachycardia, thrombophlebitis, vein disorder.

Central, peripheral nervous system: anxiety, confusion, depression, insomnia, nervousness, neuropathy.

Endocrine: hypothyroidism. A decrease in the uptake of radioactive iodine by the thyroid gland has been reported with other sulfonylurea drugs. This has not been shown with gliclazide 80 mg tablets during a study involving 15 patients.

Gastro-intestinal: abdominal pain, anal fissure, appetite increased, colitis, duodenal ulcer, epigastric fullness, faecal incontinence, flatulence, gastric irritation, gastroesophageal reflux, GI neoplasm benign, hemorrhoids, melena, dry mouth, oesophagitis, saliva increased, tooth ache, tooth disorder, vomiting. These reactions are generally dose-related and may disappear when the dose is reduced.

Hearing and vestibular: hearing decreased, tinnitus.

Liver and biliary: increased liver enzymes, hepatitis, hepatomegaly.

Metabolic and nutritional: gout, glycosuria, hypercholesterolemia, hypertriglyceridemia, thirst. Cases of hepatic porphyria and disulfiram-like reactions have been described with sulfonylurea drugs. Clinical experience to date has shown that gliclazide 80 mg tablets has a low incidence of disulfiram type reactions.

Musculo-skeletal: arthropathy, bursitis, hernia congenital, skeletal pain, spine malformation.

Reproductive: balanoposthitis, benign female breast neoplasm, impotence, mastitis, menstrual disorder, prostatic disorder, vaginitis.

Respiratory: asthma, dyspnea, tracheitis.

Skin and appendages: fungal dermatitis, eczema, erythema, hyperkeratosis, maculopapular or morbiliform rash, nail disorder, onychomycosis, pruritus, dry skin, skin ulceration, urticaria. These reactions may persist during treatment, which must be then interrupted. Cases of porphyria tarda and of photosensitivity have also been described with sulfonylurea drugs.

Urinary: albuminuria, cystitis, nocturia, polyuria, renal calculus, renal cyst.

Vision: cataract, conjunctival haemorrhage, diplopia, glaucoma, abnormal lacrimation, retinal disorder, abnormal vision, vitreous disorder, xerophthalmia.

Abnormal Hematologic and Clinical Chemistry Findings

The pattern of laboratory tests abnormalities previously observed with gliclazide 80 mg tablets was similar to that for other sulfonylureas. Occasional mild to moderate elevations of hepatic enzymes, LDH and creatinine and decrease in natremia have been observed. These abnormalities frequently encountered with treated or untreated diabetic patients are rarely associated with clinical symptoms and generally not considered to be drug related. As with all hypoglycemic sulfonylurea drugs, a few rare cases of leukopenia, agranulocytosis, thrombocytopenia and anemia have been reported with gliclazide 80 mg tablets. No laboratory tests abnormalities other than those already reported with gliclazide 80 mg tablets have been observed during controlled clinical trials performed on gliclazide modified release tablets 30 mg

Post-Market Adverse Drug Reactions

In post-marketing experience with gliclazide modified release tablets 30 mg, gastrointestinal disturbance, including abdominal pain, nausea, vomiting, dyspepsia, diarrhea and constipation have been reported. Skin and subcutaneous tissue disorders, rash, pruritus, urticaria, erythema, maculopapular rashes and bullous reactions have been more rarely reported.

The most serious adverse drug reactions reported with gliclazide are hypoglycaemic coma, pancytopenia, thrombocytopenia, hepatitis, cholestatic jaundice, pyrexia, pancreatitis acute and skin reactions (pruritus and rash).

Class attribution effects: Cases of erythrocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia and allergic vasculitis, have been described for other sulphonylureas. With other sulfonylureas cases were also observed of elevated liver enzyme levels (AST, ALT, alkaline phosphatase) 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. Discontinue treatment if cholestatic jaundice appears.

DRUG INTERACTIONS

Overview

As a result of drug interaction, hypoglycemia may be potentiated when a sulfonylurea is used concurrently with agents such as: long-acting sulfonamides, tuberculostatics, NSAIDs, fibrates, monoamine oxidase inhibitors, salicylates, probenecid, beta-blockers, azole antifungal agents (oral and parenteral preparations), H2 receptor antagonists and angiotensin converting enzyme inhibitors. In addition, hypoglycemia is potentiated when gliclazide is used in combination with other antidiabetic agents (insulin, alpha glucosidase inhibitors, biguanides) which is not indicated.

Certain drugs tend to induce hyperglycemia and may lead to loss of blood sugar control. These include diuretics (thiazides, furosemide), corticosteroids, oral contraceptives (estrogen plus progestogen), chlorpromazine, ritodrine, salbutamol, terbutaline and nicotinic acid in pharmacologic doses.

Barbiturates should be used with caution in patients receiving an oral hypoglycemic agent since they may reduce the hypoglycemic effect.

Sulfonylureas may potentiate the action of anticoagulants. Adjustment of the anticoagulant dose may be necessary.

Drug-Drug Interactions

| Gliclazide | Reference | Effect | Clinical comment |
|---|------------------|------------------------------------|---|
| Miconazole (systemic route, oromucosal gel) | C | Increases the risk of hypoglycemia | <u>Contra-indicated combination.</u> Increases the hypoglycaemic effect with possible onset of hypoglycaemic symptoms, or even coma. |

| | | | |
|--|---|------------------------------------|--|
| Phenylbutazone (systemic route) | C | Increases the risk of hypoglycemia | <u>Combination is not recommended.</u> Increases the hypoglycaemic effect of sulphonylureas (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. |
| Other antidiabetic agents (insulins, acarbose, biguanides) | C | Increases the risk of hypoglycemia | <u>Combinations requiring precautions for use.</u> Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycemia may occur. |
| Beta-blockers | C | Increases the risk of hypoglycemia | <u>Combinations requiring precautions for use.</u> Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycemia may occur. |
| Fluconazole | C | Increases the risk of hypoglycemia | <u>Combinations requiring precautions for use.</u> Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycemia may occur. |
| Angiotensin converting enzyme inhibitors | C | Increases the risk of hypoglycemia | <u>Combinations requiring precautions for use.</u> Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycemia may occur. |
| H2-receptor antagonists | C | Increases the risk of hypoglycemia | <u>Combinations requiring precautions for use.</u> Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycemia may occur. |

| | | | |
|---------------------------------------|---|--|---|
| MAOIs | C | Increases the risk of hypoglycemia | <u>Combinations requiring precautions for use.</u> Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycemia may occur. |
| Sulfonamides | C | Increases the risk of hypoglycemia | <u>Combinations requiring precautions for use.</u> Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycemia may occur. |
| Nonsteroidal anti-inflammatory agents | C | Increases the risk of hypoglycemia | <u>Combinations requiring precautions for use.</u> Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycemia may occur. |
| Danazol | C | Causes an increase in blood glucose levels | <u>Combination is not recommended because of diabetogenic effect of danazol.</u> 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. |
| Chlorpromazine (neuroleptic agent) | C | Causes an increase in blood glucose levels | <u>Combination requiring precautions during use.</u> High doses (>100 mg per day of chlorpromazine) increase blood glucose levels (reduced insulin release). Warn the patient and emphasise 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 | C | Causes an increase in blood glucose levels | <u>Combination requiring precautions during use.</u> Increase in blood glucose levels with possible ketosis (reduced tolerance to carbohydrates due to glucocorticoids). Warn the patient and emphasise the importance of blood glucose monitoring, particularly at the start of 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.) | C | Causes an increase in blood glucose levels | <u>Combination requiring precautions during use.</u> Increased blood glucose levels due to beta-2 agonist effects. Emphasise the importance of monitoring blood glucose levels. If necessary, switch to insulin. |
| Anticoagulant therapy (Warfarin and other) | C | Potential of anticoagulation | <u>Combination which must be taken into account.</u> Sulfonylureas may lead to potentiation of anticoagulation during concurrent treatment. Adjustment of the anticoagulant may be necessary. |
| Drugs containing alcohol | C | Increases the risk of hypoglycemia | Intolerance to alcohol (disulfiram-like reaction: flushing, sensation of warmth, giddiness, nausea and occasionally tachycardia) may occur in patients treated with sulfonylurea. |

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

There are no established drug-food interactions.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

This treatment should only be prescribed 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 hypoglycemia if a meal is taken late, if an inadequate amount of food is consumed or if the food is low in carbohydrate. Hypoglycemia is more likely to occur during periods of low-calorie diet and following prolonged or strenuous exercise. Intolerance to alcohol (disulfiram-like reaction: flushing, sensation of warmth, giddiness, nausea and occasionally tachycardia) may occur in patients treated with sulfonylurea. Alcohol increases the hypoglycaemic reaction (by inhibiting compensatory reactions) that can lead to the onset of hypoglycaemic coma. Avoid alcohol or medicines containing alcohol.

Treatment with GLICLAZIDE MR can have effects on ability to drive and use machines. Patients should be made aware of the symptoms of hypoglycemia and should be careful if driving or operating machinery, especially at the beginning of treatment.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Determination of the proper dosage for GLICLAZIDE MR for each patient should be made on the basis of frequent determinations of blood glucose during dose titration and throughout maintenance.

The daily dose of GLICLAZIDE MR may vary from 30 to 120 mg (1 to 4 tablets) once daily.

Recommended Dose and Dosage Adjustment

The recommended starting dose of GLICLAZIDE MR is 1 tablet per day (30 mg), even in elderly patients (over 65 years old).

A single daily dose provides effective blood glucose control. The single daily dose may be between one and three, or even four, tablets. The daily dose should not exceed 120 mg.

Dose adjustment should be carried out in steps of 30 mg, according to the blood glucose response. Each step should last for at least two weeks.

Administration

It is recommended that the medication be taken at breakfast time. The tablets should be swallowed whole and must not be chewed or crushed.

- Previously untreated patients should commence with a dose of 30 mg and will benefit from dose adjustment until the appropriate dose is reached.
- GLICLAZIDE MR can replace gliclazide 80 mg immediate release tablets.
- GLICLAZIDE MR can replace an antidiabetic treatment without any transitional period. If a patient is switched from a hypoglycemic sulfonylurea with a prolonged half-life (i.e. chlorpropamide) he/she should be carefully monitored (for 1 to 2 weeks) in order to avoid hypoglycemia due to possible residual effects of the previous therapy.

It is advisable to ascertain the contribution of the drug in control of the blood glucose level by discontinuing the medication semi-annually or at least annually with careful monitoring of the patient. If the need for the drug is not evident, the drug should not be resumed. In some diabetic subjects, short-term administration periods of the drug may be sufficient during periods of transient loss of blood sugar controls.

Geriatrics

The efficacy and tolerance of gliclazide modified-release tablets 30 mg, prescribed using the same therapeutic regimen in subjects over 65 years, has been confirmed in clinical trials. The dosage will therefore be identical to that recommended for adults under the age of 65 years.

Renal Insufficiency

The efficacy and tolerance of gliclazide modified-release tablets 30 mg, prescribed using the same therapeutic regimen in subjects with mild to moderate renal failure (creatinine clearance of between 15 and 80 mL/min), has been confirmed in clinical trials. The dosage will therefore be identical to that in subjects with normal renal function.

Patients receiving Insulin

Maturity onset diabetics with no ketoacidosis or history of metabolic decompensation and whose insulin requirements are less than 40 units per day may be considered for GLICLAZIDE MR therapy after cessation of insulin.

If a change from insulin to GLICLAZIDE MR is contemplated in such a patient, discontinue insulin for a period of 2 or 3 days to determine whether any therapy other than dietary regulation and exercise is needed. During this insulin-free interval, test the patient's urine at least 3 times daily for glucose and ketone bodies and monitor the results carefully. The appearance of significant ketonuria accompanied by glucosuria within 12 to 24 hours after the withdrawal of insulin, strongly suggests that the patient is ketosis prone, and precludes the change from insulin to sulfonylurea therapy.

Missed Dose

If a dose is forgotten, the dose taken on the next day should not be increased.

OVERDOSAGE

Symptoms

Overdosage with sulfonylureas may result in hypoglycemia but it should be noted that the dosage which causes such hypoglycemia varies widely and may be within the accepted therapeutic range in sensitive individuals.

The manifestations of hypoglycemia include sweating, flushing or pallor, numbness, chilliness, hunger, trembling, headache, dizziness, increased pulse rate, palpitations, increased blood pressure and apprehensiveness in mild cases. In more severe cases, coma appears.

However, symptoms of hypoglycemia are not necessarily as typical as those described above and sulfonylureas may cause insidious development of symptoms mimicking cerebrovascular insufficiency.

Treatment of Overdosage

Discontinue medication and treat hypoglycemia by giving dextrose promptly and in sufficient quantity. Some sulfonylurea-induced hypoglycemias may be refractory to treatment and susceptible to relapse especially in elderly or malnourished patients. Continuous dextrose infusions for hours or days have been necessary. 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. For management of a suspected overdose, contact your Regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

GLICLAZIDE MR (gliclazide) is a hypoglycemic agent of the sulfonylurea group. The hypoglycemic action of GLICLAZIDE MR is related to an improvement in insulin secretion from the functioning beta cells of the pancreas. It potentiates the insulin release, improves the dynamics of insulin. Increase in postprandial insulin and C-peptide secretion persists after two years of treatment. Gliclazide has extra-pancreatic actions. These metabolic actions are accompanied by hemovascular effects. However, the mechanism of action regarding these effects is still poorly understood. The clinical significance of these effects has not been established.

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.

Extra-pancreatic effects. It has been demonstrated that gliclazide increases peripheral insulin sensitivity:

- In muscle: the action of insulin on glucose uptake, measured during an euglycemic hyperinsulinemic clamp is significantly increased (+35%), due to an improvement in peripheral sensitivity to insulin. This leads to an improvement in diabetes control. Gliclazide acts mainly by potentiating insulin action on muscle glycogen synthetase. Moreover, results of studies on the muscle are consistent with a post-transcriptional action of gliclazide on GLUT4 glucose carriers;
- In the liver: studies on glucose turnover show that gliclazide decreases hepatic glucose production, leading to an improvement in fasting blood glucose levels.

Hemovascular effects. 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):
- A restoration of the vascular endothelium fibrinolytic activity with an increase in t-PA activity.

Antioxidant effects. A controlled clinical study in diabetics has confirmed the antioxidant effects of gliclazide that were already demonstrated in clinical pharmacology: reduction in plasma levels of lipid peroxides, increase in the activity of erythrocyte superoxide dismutase.

Pharmacodynamics

Hypoglycemic activity

The main mechanism of action of gliclazide consists in an increase in the insulin secretory potential of pancreatic beta-cells in a situation of hyperglycemia. This effect of gliclazide on

insulin secretion is maintained during long-term treatment in type 2 diabetic patients. It was observed that the administration of gliclazide was followed by:

- a consistent and significant decrease in fasting blood glucose;
- a more than 1% decrease in mean glycated hemoglobin;
- an inhibition by 12 to 27% of the rise in blood glucose after a standard meal or an oral glucose load.

A slight and transitory increase in mean fasting plasma insulin levels was occasionally observed with gliclazide treatment.

Regarding the biphasic nature of insulin secretion, the first peak, that is severely blunted in type 2 diabetes, is improved during gliclazide treatment.

In addition to the effect of gliclazide on the secretion of insulin, extrapancreatic effects have also been evidenced. Gliclazide improves peripheral sensitivity to insulin and increases glucose utilization rate:

- with euglycemic hyperinsulinemic clamps in obese and non-obese type 2 diabetic patients, it has been shown that gliclazide, after 3 months of treatment, increases the disappearance rate and metabolic clearance of glucose at the highest insulin infusion rates (100 and 300 mU/kg/h);
- in comparison to diet treatment, gliclazide also enhances insulin-stimulated glucose metabolism after 8 weeks of treatment by potentiating insulin action on skeletal muscle glycogen synthetase.

Studies on glucose turnover have also shown that basal hepatic glucose production, measured by tracer methodology, was markedly reduced (28-50%) after 3 months of treatment.

Hemovascular activity

Gliclazide possesses anti-platelet properties which are independent of its antidiabetic action, and improves the fibrinolytic potential in diabetic patients:

- numerous studies have shown inhibitory effects of gliclazide on platelet aggregation and hyperadhesiveness.

A statistically significant 22% decrease in collagen-induced platelet aggregation has been observed after 3 and 6 months of treatment with gliclazide in 15 patients previously well controlled under glibenclamide. A concentration-dependent inhibition of PAF-induced platelet aggregation has also been reported with gliclazide in vitro in platelet-rich plasma from healthy subjects and type 2 diabetic patients. Finally, a consistent decrease in markers of platelet activation (e.g. beta thromboglobuline and thromboxane B2 levels) has been observed with gliclazide whether glycemic control improved or not; change to gliclazide of patients treated since several years by chlorpropamide is followed by normalisation of the t-PA activity, sustained over 24-48 months. This has been confirmed by 2 studies in type 1 and glibenclamide treated type 2 diabetics: in both, the addition of gliclazide to insulin or the switch to this sulfonylurea were followed by significant increase in t-PA and in the activity of the intrinsic fibrinolytic system.

Antioxidant activity

Gliclazide is a strong free radical scavenging agent, an effect demonstrated both in vitro and in patient. In 17 type 2 diabetic patients switched to gliclazide and seen at regular intervals during a 36-week period, peroxidized lipids and oxidized damaged IgG decreased significantly. These effects of gliclazide on the oxidative stress have been confirmed in a double-blind study in diabetic patients. Highly significant and sustained decrease in peroxidized lipid levels and increase in erythrocyte superoxide dismutase activity were obtained with gliclazide, but not with glibenclamide.

Pharmacokinetics

The initial development of gliclazide led to the marketing of two different formulations of 80 mg tablets worldwide, with only one formulation being registered in each country. Although the two formulations differed substantially in their pharmacokinetic performance in vivo, there was no evidence that they were different in their efficiency and safety in type 2 diabetic patients, thus

suggesting that gliclazide does not exert its effect in a dose-dependent manner but by virtue of a threshold plasma drug concentration. Both formulations of gliclazide are prescribed in the dose range 80-320 mg per day, tablets being taken once to 3-times daily. Individual dose requirements vary between patients, which most likely reflect the inter-individual variability in pharmacokinetic characteristics in addition to differences in diabetes severity. Also the noted variability in prescribed average dose between countries may partly be explained by differences in the marketed pharmaceutical formulation. It was therefore essential to develop a new standardized pharmaceutical formulation for worldwide use, presenting optimal and consistent release characteristics. Furthermore, it was thought that a medication suitable for once-daily administration would be desirable. These considerations led to the development of a *new* modified release formulation of gliclazide.

Gliclazide is slowly and completely absorbed from the gastro-intestinal tract and plasma levels increase progressively, resulting in a plateau-shaped curve from the sixth to the twelfth hour after administration of gliclazide modified release tablets 30 mg. Intra-individual variability is low. Food intake does not affect the rate and extent of absorption. The relationship between the dose administered and the area under the concentration curve as a function of time is linear. In man it is highly bound to plasma proteins, about 95 %. The mean elimination half life in man approximates 16 hours. A single daily dose of gliclazide modified release tablets 30 mg maintains effective gliclazide plasma concentrations over 24 hours. No clinically significant modifications in the pharmacokinetic parameters have been observed in elderly patients.

Following oral administration the unchanged gliclazide in plasma is extensively metabolized with little of the unchanged compound (< 1%) appearing in the urine. No active metabolites have been detected in plasma. Gliclazide metabolites and conjugates are primarily eliminated via kidneys 60 to 70%, and about 10 to 20% via feces. Six principal metabolites have been identified in urine, essentially oxidized and hydroxylated derivatives, and two glucuronoconjugates.

Absorption:

The absorption of gliclazide from gliclazide modified release tablets 30 mg is slow and complete

(mean absolute bioavailability of 97%) and is not affected by simultaneous food intake. Plasma concentrations rise gradually and the maximum concentration is usually reached after about 6 hours, with a plateau maintained for another 4 to 6 hours.

Distribution:

The volume of distribution is relatively small which can partially be explained by high protein binding (about 95 %).

Metabolism:

Although more than 90% of unchanged gliclazide is found in plasma following administration, this is intensively metabolized with little of the unchanged compound (<1%) found in urine. Six principal metabolites have been found in urine, essentially oxidized and hydroxylated derivatives, and two glucuronoconjugates. No active metabolites have been detected in plasma. The principal metabolic pathways of gliclazide may be summarized as shown hereafter.

Excretion:

Gliclazide is essentially eliminated via the urine: 60 to 70% as against 10 to 20% via feces. The mean elimination half life is 16 h (range 12-20 h). Linear kinetics were observed with gliclazide modified release tablets 30 mg in the dose range up to 90 mg.

Special Populations and Conditions

Pediatrics:

Safety and effectiveness of GLICLAZIDE MR in children have not been established. GLICLAZIDE MR is therefore not recommended for use in children and adolescents.

Gender:

No significant relationship was found between any of the pharmacokinetic parameters and the covariables gender, body weight and creatinine clearance.

STORAGE AND STABILITY

Store at room temperature (15°C - 25°C). Protect from humidity.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage form:

GLICLAZIDE MR (gliclazide modified release tablets) 30 mg: White, to off-white, flat-faced, bevelled edge, capsule shaped tablets, engraved “30” on one side and plain on the other side.

Composition:

Each tablet (90 mg) contains:

active principle: 30 mg gliclazide

excipients: colloidal silicon dioxide
 hydroxypropyl methylcellulose
 stearic acid

Packaging:

GLICLAZIDE MR is available in bottles of 100.

CLINICAL TRIALS

Two pivotal controlled clinical studies involving a total of 888 type 2 diabetic patients have been conducted during the development of the modified release (MR) formulation of gliclazide.

The first study was a phase II, multicentre, comparative, randomized, double-blind trial designed to evaluate the dose/efficacy relationship of the MR formulation administered once daily and to determine its minimum effective dose. Placebo and five gliclazide MR doses (15, 30, 60, 90 and 135 mg) were assessed over 8 weeks in 224 patients (35 to 39 patients per group). The lowest tested dose (15 mg once daily) slightly decreased fasting plasma glucose (FPG) but the effect of this dose on glycated hemoglobin (HbA_{1c}) was not clinically significant. The first gliclazide MR dose demonstrating clinically relevant efficacy on both parameters was 30 mg once daily. For doses above 30 mg, the efficacy of the gliclazide MR formulation was confirmed with a good clinical and biological acceptability. This study thus demonstrated that 30 mg of gliclazide MR administered once daily is the minimum effective dose for initiating treatment in type 2 diabetic patients.

The second study was a large phase III, multinational, comparative, randomized, double-blind trial aimed at demonstrating the therapeutic equivalence of gliclazide MR compared to the gliclazide 80 mg conventional formulation marketed in Canada. A total of 664 patients were randomized in two parallel groups, one assigned to gliclazide 80 mg (336 patients) and one to gliclazide MR (328 patients). After a 4-month dose escalating period allowing patient-tailored titration, patients entered a maintenance period of 6 months. Gliclazide 80 mg was administered at 80, 160, 240 or 320 mg/day, with doses above 80 mg given twice daily; gliclazide MR was always administered once daily at breakfast time at 30, 60, 90 or 120 mg/day. The study demonstrated that after 10 months of treatment, gliclazide MR is at least as effective as gliclazide 80 mg in controlling HbA_{1c} and FPG levels of type 2 diabetic patients. The therapeutic equivalence was actually achieved with lower daily doses of the MR formulation, 30 mg of gliclazide MR producing a similar effect as 80 mg of gliclazide conventional formulation. The general safety of both formulations was good with no difference in type and incidence of adverse

events. With regard to hypoglycemia, the number of patients experiencing hypoglycemic episodes was almost the same in both groups. However, the number of hypoglycemic episodes was lower in the gliclazide MR group than in the gliclazide 80 mg group.

Comparative Bioavailability Studies

Comparative bioavailability studies were conducted under fasting and fed conditions, using GLICLAZIDE MR, and the reference product, Diamicon[®] MR (manufactured by Servier Canada Inc.). The study consisted of a randomized, single dose (1 x 30 mg gliclazide), crossover design, with two treatments and two periods. Nineteen (19) healthy male/ female volunteers completed each study in its entirety.

Summary Table of the Comparative Bioavailability Data

| Gliclazide (A single 30 mg dose: 1 x 30 mg) From Measured Data/Fasting Conditions Geometric Least Square Mean Arithmetic Mean (CV%) | | | | |
|---|---------------|---------------------------------------|--|---|
| Parameter | Gliclazide MR | Diamicon [®] MR [†] | Ratio of Geometric Means (%) ^{##} | 90% Confidence Interval (%) ^{##} |
| AUC _t (ng•h/mL) | 17742.5 | 16957.3 | 104.6 | 99.8 – 109.7 |
| | 18962.0 (42) | 18200.9 (44) | | |
| AUC _{inf} (ng•h/mL) | 18910.2 | 18135.2 | 104.3 | 99.7 – 109.1 |
| | 20810.1 (54) | 20092.3 (58) | | |
| C _{max} (ng/mL) | 643.2 | 718.2 | 89.6 | 83.1 – 96.5 |
| | 667.6 (28) | 738.9 (21) | | |
| T _{max} [#] (h) | 12.74 (43) | 9.06 (26) | | |
| T _{half} [#] (h) | 15.68 (37) | 16.60 (38) | | |
| [#] Arithmetic means (CV%) only. ^{##} Based on the least squares estimate. [†] Diamicon [®] MR is manufactured by Servier Canada Inc., and was purchased in Canada. | | | | |

Summary Table of the Comparative Bioavailability Data

| Gliclazide (A single 30 mg dose: 1 x 30 mg) From Measured Data/Fed Conditions Geometric Least Square Mean Arithmetic Mean (CV%) | | | | |
|---|-------------------------|---------------------------------------|--|---|
| Parameter | Gliclazide MR | Diamicon [®] MR [†] | Ratio of Geometric Means (%) ^{##} | 90% Confidence Interval (%) ^{##} |
| AUC _t (ng•h/mL) | 16072.1 16643.3 (27) | 16165.9 16718.9 (28) | 99.4 | 95.4 – 103.6 |
| AUC _{inf} (ng•h/mL) | 16860.1 17626.2 (33) | 17140.0 18154.4 (42) | 98.4 | 93.9 – 103.1 |
| C _{max} (ng/mL) | 853.5 876.2 (23) | 962.6 987.3 (21) | 88.7 | 80.6 – 97.6 |
| T _{max} [#] (h) | 6.43 (24) | 6.11 (37) | | |
| T _{half} [#] (h) | 14.51 (31) | 15.37 (49) | | |
| [#] Arithmetic means (CV%) only. ^{##} Based on the least squares estimate. [†] Diamicon [®] MR is manufactured by Servier Canada Inc., and was purchased in Canada. | | | | |

A comparative bioavailability study was conducted under fasting steady-state conditions, using GLICLAZIDE MR, and the reference product, Diamicon[®] MR (manufactured by Servier Canada Inc.). The study consisted of a randomized, single dose (1 x 30 mg gliclazide at time zero (0) and every 24 hours thereafter for the next 5 days [24, 48, 72, 96 and 120 hours] for each period of the study), crossover design, with two treatments and two periods. Eighteen (18) healthy male/ female volunteers completed this study in its entirety.

Summary Table of the Comparative Bioavailability Data

| Gliclazide (Multiple dose: 1 x 30 mg) From Measured Data/Steady State Geometric Mean ^{##} Arithmetic Mean (CV%) | | | | |
|--|-------------------------|--|--|---|
| Parameter | Gliclazide MR | Diamicron [®] MR [†] | Ratio of Geometric Means (%) ^{##} | 90% Confidence Interval (%) ^{##} |
| AUCtau (ng•h/mL) | 19093.4 19935.8 (33) | 18855.0 19329.8 (24) | 101.3 | 94.3 – 108.7 |
| Cmax (ng/mL) | 1067.1 1107.5 (30) | 1138.4 1162.5 (22) | 93.7 | 86.0 – 102.2 |
| Cmin (ng•h/mL) | 456.5 509.0 (49) | 471.9 497.9 (36) | 96.7 | 83.2 – 112.4 |
| Tmax# (h) | 7.71 (47) | 7.65 (32) | | |
| Fluc# (%) | 75.6 (26) | 84.7 (19) | | |
| [#] Arithmetic means (CV%) only. ^{##} Based on the least squares estimate. [†] Diamicron [®] MR is manufactured by Servier Canada Inc., and was purchased in Canada. | | | | |

DETAILED PHARMACOLOGY

ANIMAL PHARMACOLOGY

Pharmacokinetics and Metabolism

This has been studied in four animal species (monkey, dog, rabbit and rat) after single or repeated oral administration of gliclazide. The principal characteristics are shown in the table below.

| BLOOD KINETICS OF GLICLAZIDE (PO) IN DIFFERENT SPECIES (single doses) | | | | | | | |
|---|----------------------------|-------------------------------|------------------|--|-------------------|----------------------|------------------|
| Species | Number of subjects (doses) | Absorption T ₂ (h) | Plasma peak (h) | Volume of distribution (% body weight) | | Plasma half-time (h) | |
| Monkey | 4 3 and 50 mg/kg | 0.3 ¹ | 1-2 ¹ | 24.4 ¹ | 108 ⁴ | 2.9 ¹ | 6.2 ⁴ |
| Beagle | 3 3 and 50 mg/kg | 0.7 ¹ | 2-6 ¹ | 21.3 ¹ | 22 ⁴ | 10.7 ¹ | 9.9 ⁴ |
| Rabbit | 5 10 and 25 mg/kg | 0.7 ² | 3 ² | 30.8 ² | 51.8 ³ | 3.9 ² | 5.9 ³ |
| Rat | 5 10 mg/kg | 0.5 ² | 1 ² | 53.8 ² | - | 2.5 ² | - |

¹ = 3 mg/kg PO

² = 10 mg/kg PO

³ = 25 mg/kg PO

⁴ = 50 mg/kg PO

Gliclazide is rapidly absorbed in all species, with a plasma peak observed between 1 and 6 hours. More than 90% of gliclazide is found unchanged in the plasma. Elimination from plasma is monophasic with inter-species variations concerning half-life.

Excretion is similar in all species with 60 to 70% of the dose found in urine and 10 to 20% in feces.

The drug is extensively metabolized into at least 5 metabolites and only small amounts of unchanged compound are excreted in the urine.

Hypoglycemic activity

The hypoglycemic action of gliclazide has been observed in the rat, rabbit, guinea-pig and dog following intravenous or oral administration. The degree and duration of these effects are dose dependent.

Comparison of ED 30 shows that gliclazide is 9 times more active than tolbutamide in the rabbit and 25 times more active in the rat. The duration of action of gliclazide is also greater than that of tolbutamide.

Gliclazide stimulates the insulin secretion and particularly restores the early peak in the isolated perfused pancreas of diabetic rats.

This insulintropic action is related to the transfer of calcium into the pancreatic cell. Gliclazide is not involved in the biosynthesis of insulin induced by glucose but modifies the distribution of calcium in isolated rat pancreas cells.

At the extrapancreatic level, gliclazide potentialises the action of insulin on the glucose intracellular transfer and influences its oxidation on an isolated adipocyte model when insulin is present in the medium.

Hemovascular activity

Gliclazide delays the development of the mural thrombus formed after electrical lesion of the vascular endothelium in the rat and increases its disaggregation speed.

In dog, gliclazide prevents the formation of capillary ADP-induced platelet aggregates at the retinal level.

These properties can be explained by its action on:

- the platelet behavior: reduction of the platelet adhesiveness in the diabetic rabbit and of platelet aggregation induced by ADP or by collagen in the rabbit;
- the prostaglandin equilibrium: inhibition of the acid arachidonic release and in vitro thromboxan synthesis and increase in the PGI₂ production;
- the parietal fibrinolysis: increase in the release of the parietal plasminogen activator (t-PA). This activator of endothelial origin, acts on plasmin which is the enzyme degrading fibrin.

Gliclazide improves vascular function in diabetic animals by preventing the abnormal contracting effect of acetylcholine after NO synthesis inhibition. Protective properties of gliclazide on capillary permeability have also been demonstrated in the cheek pouch model in streptozotocin-diabetic Syrian hamsters.

Long-term treatment of diabetic sand rats with gliclazide prevents development of arterial lesions.

Other actions

Gliclazide has no action on the central nervous system, autonomic nervous system nor respiratory, gastro-intestinal systems.

Treatment of streptozotocin-diabetic rats with gliclazide has shown a significant improvement in heart function.

TOXICOLOGY

Acute toxicity

| Species | Mean Weight | Number of animals per lot | LD ₅₀ (mg/kg) | |
|-------------------------|-------------|---------------------------|--------------------------|---------------------|
| Mouse CD-SPF | 25 g | 10 M 10 F | > 3000 | |
| Mouse ICR-HAN | 20 g | 10 M 10 F | > 4000 | |
| Rat SD-SPF | 250 g | 10 M | 3733 < 5200 2679 | |
| | | 10 F | 3407 < 5467 2123 | |
| Rat CFY | 110 g | 6 M 6 F | > 4000 | |
| Tricolour Guinea Pig | 240 g | 4 M | 48 hours | 10 days |
| | | | 1732 < 1999 1501 | 1599 < 2016 1269 |
| | | 4 F | 2244 < 2509 1944 | 2068 < 2553 1675 |
| Beagle Dog | 7 kg | 3 M 3 F | > 3000 | |

The LD₅₀ is greater than 3000 mg/kg in the mouse, rat and dog (i.e. 300 times the therapeutic dose) and than 2000 mg/kg in the guinea-pig (i.e. 500 times the therapeutic dose).

Symptomatology is essentially linked to the hypoglycemic effect of the drug.

Sub-chronic Toxicity

– Maximum tolerated dose:

In the dog, this dose is between 150 and 200 mg/kg by daily administration.

- Four-week oral toxicity study in the Beagle dog:
Groups of 4 Beagle dogs (2 males, 2 females), were treated for 30 days with 0, 15, 30, 45 or 90 mg/kg/day. At the dose of 90 mg/kg, 2 animals died as a result of prolonged hypoglycemic coma following 2 weeks of treatment. All others showed normal behaviour, with the exception of an increase in the weight of the liver. No evidence was found of any change in biochemical (apart from the fall in blood glucose), hematological and histopathological parameters.

- Two-month oral toxicity study in the guinea-pig:
Groups of 10 guinea-pigs (5 males, 5 females), were treated 6 days out of 7 for 2 months with 0, 25, 50 or 100 mg/kg/day. Only male animals in the 50 mg/kg group showed delayed weight gain. All others had normal biochemical, hematological and histopathological results.

Chronic Toxicity

- Six-month study in the Sprague-Dawley rat:
Groups of 20 rats (10 males, 10 females) weighing 300 g, were treated for 6 days out of 7 for 6 months with 0, 25, 100 or 200 mg/kg/day. Seven deaths occurred as a result of technical problems. All other animals showed normal behaviour and haematological results. From a biochemical standpoint, blood urea decreased significantly in the male rats as did blood glucose in the males of the 100 mg/kg/day group. Histological examination showed an increase in the weight of the liver and kidneys in male animals, not accompanied by any histological lesion.

A six-month rat study carried out in Japan with higher doses (50, 100, 200, 400 and 800 mg/kg) indicates a possible higher sensibility in the female to the product: slight increases in liver enzymes together with slight decreases in erythrocytes counts, hematocrit values and hemoglobin concentrations at doses of 200 mg/kg and higher.

- Six-month study in the Beagle Dog

Groups of 6 dogs (3 males, 3 females) were treated daily for 6 months with 15 or 30 mg/kg of gliclazide or 50 mg/kg of tolbutamide.

From a clinical standpoint:

- 3 deaths (one at 15 mg/Kg, two at 30 mg/Kg) in the gliclazide group as a result of hypoglycemic coma;
- 1 convulsion, 4 cases of severe gastro-intestinal disturbances in the tolbutamide group;
- Weight changes and food consumption were similar with both drugs.

From a laboratory standpoint:

- 40% fall in blood glucose in animals treated with gliclazide.
- Signs of hepatotoxicity in the tolbutamide group.

From a histological standpoint:

- Increase in weight of the liver in the 3 deaths of the gliclazide group.
- Increase in the weight of the liver and lesions of toxic hepatitis in 5 animals out of 6 of the tolbutamide group.

– Twelve-month oral toxicity study in the Beagle Dog

Groups of 8 dogs (4 males, 4 females) were treated for 12 months with 0, 12 or 24 mg/kg/day of gliclazide. Four animals in each group were sacrificed after 90 days.

- there were no deaths;
- no evidence of any modification in behaviour and body weight;
- significant fall in blood glucose;
- fluctuation in certain parameters (liver enzymes, lipid profile, creatinine);
- at autopsy: swelling of the renal and hepatic parenchyma and at the highest dose a slight increase in the weight of the thyroid and slight decrease in the weight of the pituitary gland.

– Twelve-Month Oral Toxicity Study in the Rhesus Monkey

Groups of 8 rhesus monkeys (4 males, 4 females) were treated daily for 12 months with 0, 20, 60 or 180 mg/kg of gliclazide.

- no evidence was found of any modification in weight gain nor food consumption;
- significant fall in blood glucose;
- irregular rise in some liver enzymes in some animals;
- no abnormality by histopathological examination.

Teratogenicity

Teratogenicity studies have been carried out in three species: mouse, rat and rabbit.

- In the CD/SPF mouse (group of 30 females), administration of gliclazide at doses of 0, 50, 200 and 500 mg/kg/day starting from mating and throughout gestation did not modify fertilization and abortion rates and had no apparent teratogenic effect.
- In the CFY-SPF rat (groups of 20 females), administration of gliclazide at doses of 0, 50, 100 and 200 mg/kg/day from the 6th to the 15th day of gestation did not show any embryotoxic effect.
- In the SD/SPF rat (groups of 60 females), administration of gliclazide at the doses of 0, 15, 30, 60, 120, 240 and 480 mg/kg/day throughout gestation had no effect on fertilization, gestation, mean number of fetuses or incidence of fetal abnormalities. The number of offspring surviving at 48 hours was decreased in the 15, 60, 120 and 480 mg/Kg groups. No other abnormality was seen.
- In the common rabbit (group of 15 females), administration of gliclazide at doses of 0, 10, 25 and 50 mg/kg/day from the 6th to the 18th day of gestation had no effect on the number of fetal resorptions, percentage of abortion nor the mean number of fetuses per litter.
- In the New Zealand rabbit (group of 6 females), administration of gliclazide at doses of 0, 50, 75, 100 and 200 mg/Kg/day for 13 days followed by an observation period of 8 days, was associated with maternotoxicity and embryotoxicity in the form of gastro-intestinal and renal

lesions accompanied by anorexia and weight loss. However, there was no evidence of any teratogenic effect.

Fertility and reproduction

- In the SD rat, groups of 40 females and of 20 males were treated for 8 and 70 days respectively, before mating and until weaning in the females, and until 15 days after littering in the males, with gliclazide at doses of 0, 10, 50 and 200 mg/Kg/day.

There was no evidence of any change in fertilization nor abortion rates. Fetal resorption, placental hemorrhage and fetal atrophy rates were unaffected. The genital tract of treated parents showed no abnormality imputable to treatment. No embryotoxic effect was seen on fetuses of females sacrificed before littering. In females in which gestation was allowed to run to term, a significant decrease in the viability of offspring was seen at 48 hours. No abnormality was seen during the study of fertility and reproduction in first generation offspring born of treated animals.

Mutagenicity of gliclazide

The mutagenic potential of gliclazide has been sought using six mutagenesis tests, i.e.:

- 2 gene mutation tests (Ames test);
- 1 in vitro chromosomal aberration test (human lymphocyte test);
- 2 in vivo chromosomal tests (micronucleus test);
- 1 unscheduled DNA synthesis test.

Gene mutation tests

Ames Test

1st test

In this test, gliclazide was used in the presence of 5 strains of *Salmonella typhimurium* (TA 1535/1537/1538/98/100) at the doses of 0, 0.005, 0.01, 0.05, 0.1, 0.5, 1, 3, 5 and 8 mg/petri dish, with and without metabolic activators. Positive controls were used for each strain with and without metabolic activators. The qualitative test showed no mutagenic effect. The quantitative

test at doses of 0.005 mg to 8 mg/dish showed no significant increase in the number of revertants.

Thus no mutagenic effect was seen under the experimental conditions adopted.

2nd test

This test used 7 strains of *Salmonella typhimurium* (TA 97/98/100/102/ 1535/1537/1538) at the doses of 0, 0.05, 0.1, 0.5, 1, 3, 5 and 8 mg of gliclazide per petri dish, in the presence and absence of metabolic activator. Positive controls were used for each strain, with and without metabolic activators.

No mutagenic effect was seen in the qualitative test. No mutagenic activity was detected in the quantitative test under the experimental conditions described.

In vitro chromosomal aberration test

Possible clastogenic potential action of gliclazide on activated lymphocytes in culture was studied by the human lymphocyte test with and without metabolic activators. Maximum tolerated doses determined in the preliminary toxicity test were 0.033 mg/ml with metabolic activators and 0.1 mg/ml without metabolic activator.

Gliclazide was used at the following concentrations:

- 0, 0.003, 0.01 and 0.033 mg/ml with metabolic activators;
- 0, 0.01, 0.033 and 0.1 mg/ml without metabolic activator.

Cyclophosphamide (0.02 mg/ml) and bleomycin (0.250 mg/ml) were used as positive controls with and without metabolic activators. Gliclazide was not found to have any clastogenic activity under the experimental conditions described.

In vivo chromosomal aberration

Micronucleus Test:

1st Test

The test used three groups of 10 OF1 mice: 1 negative control, 1 gliclazide high dose (2 g/kg x 2), 1 gliclazide low dose (1 g/kg x 2) and one group of 5 positive control mice given cyclophosphamide (50 mg/kg x 2). No evidence was found of any significant variation in the number of erythrocyte micronuclei. Gliclazide was not associated with any mutagenic action detectable by the micronucleus test.

2nd test

The test used SPF Swiss mice as follows:

- 24 mice for the preliminary toxicology test which determined the maximum administrable dose as 3 g/kg;
- 108 mice in the phase 1 genetic toxicology test with study of effect/time relationship at the maximum administrable dose (MAD) (sacrifice of animals at times 24, 48 and 72 hours);
- 60 mice in the phase 2 genetic toxicology test with study of the dose/effect relationship at the time defined in phase 1 (t = 24 h) and using the following doses: 0, 750 (MAD/4), 1500 (MAD/2) and 3000 mg/Kg (MAD).

Cyclophosphamide 50 mg/kg was used as positive control. Gliclazide was found to be free of any clastogenic activity under the experimental conditions adopted in this trial involving oral administration in the Swiss mouse.

Unscheduled DNA synthesis

The potential of gliclazide to induce unscheduled DNA synthesis in the liver of orally dosed male Wistar rats was investigated using an in vivo/in vitro procedure. Doses of 0, 632.5 and 2000 mg/kg of gliclazide were administered by gavage. Two samples were planned and collected approximately 12-14 h or 2-4 h after dosing. Primary cultures of hepatocytes were prepared from 3 animals per dose. In vitro, the aim was to determine the net grain count. Plasma levels of gliclazide were measured 2 hours after dosing with 2000 mg/kg. Under the conditions of this study, gliclazide did not induce unscheduled DNA synthesis in rats properly exposed to the drug.

Mutagenicity of paratoluenesulfonamide (PTS)

PTS is a gliclazide degradation impurity which may occur in the dosage form. The mutagenic potential of PTS is well documented in the literature since this compound is also a degradation product of saccharin. The following in vitro and in vivo tests support the qualification of this impurity:

In vitro tests

Ames test

Strains of Salmonella typhimurium (TA 1530/1535/1538/98/100) were tested for doses $\leq 4.10^{-2}$ M. No mutagenic effect was observed. The same result was reported for the strains TA 1535/1537/1538/98/100 at doses up to 18000 μg /plate, with and without metabolic activation. In a ZLM medium (with lower content of glucose and citrate) with a metabolic activator, PTS induced a slight increase over the revertant frequency in the strain TA 98 at doses ≥ 9600 μg /plate.

SCE test on CHO-K1 cells

Concentrations of 0, 14, 200 and 400 μg /ml did not show any significant difference after a 24-hour treatment in comparison with the DMSO at a concentration of 50 μg /ml.

Test on human embryo cells

The RSa cells (ouabain-resistant) were exposed to PTS concentrations ≤ 1800 μg /ml. In comparison with a UV exposure, used as a positive control, no induction of mutation to ouabain-resistance was observed after a 24-hour treatment.

In vivo tests

Drosophila test

No mutagenic effect was reported with PTS administered by abdominal injection at a dose of 5 mM. In one study, an induction of recessive lethal sex-linked mutation was observed at a concentration of 2.5 mM.

Micronucleus test

No significant increase in the micronuclei rate was reported after intraperitoneal or oral administration (2 x 855 mg/kg) in male and female mice.

Carcinogenicity studies

Specific carcinogenicity studies have not been performed; the following safety data are now available:

- gliclazide belongs to the chemical class of the phenylsulfonylurea which do not demonstrate any mutagenic or carcinogenic potential. Its metabolic pathway is consistent with the general metabolic pathway of the class;
- gliclazide was not associated with any mutagenic action in the numerous studies performed;
- long term toxicity studies did not reveal any evidence of carcinogenicity;
- gliclazide has been studied in several thousands of patients during clinical trials and has been marketed for numerous years all over the world and in particular in Europe and Japan without any suspicion of carcinogenicity.

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PART III: CONSUMER INFORMATION

Pr GLICLAZIDE MR Gliclazide modified release tablets

This leaflet is part III of a three-part "Product Monograph" published when GLICLAZIDE MR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about GLICLAZIDE MR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

GLICLAZIDE MR is used to lower blood glucose level in adult patients with type 2 diabetes mellitus in addition to proper diet, exercise and weight reduction.

What it does:

GLICLAZIDE MR belongs to the family of hypoglycemic (antidiabetic) drugs and part of a sub family of medicines called sulfonylureas. It helps improving insulin secretion in the body.

When it should not be used:

GLICLAZIDE MR is contraindicated (must not be taken):

- If you are allergic or hypersensitive to gliclazide, other sulfonylureas, sulfonamides, or to any of the excipients of this product.
- If you have unstable and/or insulin-dependant diabetes mellitus, juvenile diabetes (type I diabetes), diabetes ketoacidosis, diabetes pre-coma and coma.
- If you are in stressful conditions such as serious infection, trauma or surgery.
- If you have severe liver disease or renal impairment.
- If you receive treatment with miconazole.
- If you are pregnant and/or breast-feeding.

What the medicinal ingredient is:

Gliclazide

What the important nonmedicinal ingredients are:

Colloidal silicon dioxide, hydroxypropyl methylcellulose and stearic acid

What dosage forms it comes in:

GLICLAZIDE MR comes in modified release tablets. Each tablet contains 30 mg of gliclazide.

WARNINGS AND PRECAUTIONS

BEFORE you use GLICLAZIDE MR talk to your doctor or pharmacist if:

GLICLAZIDE MR may cause low blood sugar (hypoglycemia). You should ask your doctor, pharmacist or diabetes educator about symptoms of low blood sugar and what to do if you experience these symptoms. You should also test your blood sugar as instructed by your doctor.

Before you use GLICLAZIDE MR talk to your doctor or pharmacist if:

- you have or have had liver, kidney disease
- you are pregnant or planning to get pregnant
- you are breast-feeding

GLICLAZIDE MR is not recommended for use in children under 18 years of age.

Driving and Operating Machinery:

Alertness and reactions may be impaired due to low blood sugar (hypoglycemia), especially at beginning of the treatment. This may affect your ability to drive or to operate machinery.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with GLICLAZIDE MR include:

other antidiabetic agents (insulin, alpha glucosidase inhibitors, biguanides), long-acting sulfonamides, tuberculostatics, NSAIDs, fibrates, monoamine oxidase inhibitors, salicylates, probenecid, beta-blockers, azole antifungal agents (miconazole and fluconazole via oral and parenteral preparations), H2 receptor antagonists and angiotensin converting enzyme inhibitors, anticoagulants, and barbiturates.

Certain drugs tend to induce hyperglycemia and may lead to loss of blood sugar control. These include diuretics (thiazides, furosemide), corticosteroids, oral contraceptives (estrogen plus progestogen), chlorpromazine, ritodrine, salbutamol, terbutaline, danazol and nicotinic acid in pharmacologic doses.

Do not take any other medicine, unless prescribed or approved by your doctor. If you require medical assistance, inform the medical practitioner that you are taking GLICLAZIDE MR.

Avoid drinking alcoholic beverages and taking medicines containing alcohol while you are taking GLICLAZIDE MR as it can lead to drop in blood sugar (hypoglycemia).

PROPER USE OF THIS MEDICATION

Usual dose:

The recommended starting dose of GLICLAZIDE MR is 1 tablet per day (30 mg), even in elderly patients (over 65 years old). The daily dose should not exceed 120 mg.

Take GLICLAZIDE MR once daily at breakfast. Swallow the tablet whole with a glass of water. The tablet must not be chewed or crushed.

You will test your sugar level as directed by your physician to make sure that your blood sugar is being controlled. Your physician should check your progress at regular visits, especially during the first few weeks that you take this medicine.

Overdose:

Taking too much of any medicines can be dangerous. If you take too many GLICLAZIDE MR tablets at once, call your doctor or go to the emergency room of your local hospital or to the nearest Poison Control Centre.

Missed Dose:

If you miss a dose of this medicine, you should not double the dose on the next day.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with any type of medication, GLICLAZIDE MR is associated with some side effects. It may, however, affect different people in different ways.

The more frequently side effects reported during clinical trials with GLICLAZIDE MR were hypoglycemia (low blood sugar) and indigestion or stomach upsets (diarrhea, constipation, nausea, vomiting, gastritis, flatulence, dyspepsia).

You should know that the usual signs of low blood sugar level (hypoglycemia) are: anxious feeling, drowsiness, chills, cold sweats, confusion, cool pale skin, difficulty in concentration, excessive hunger, fast heartbeat, headache, nausea, nervousness, shakiness, unsteady walk, unusual tiredness or weakness. If you recognize by some of these signs of the drop in blood sugar, immediately eat or drink something containing sugar and notify your doctor without delay. Good sources of sugar are: orange juice, corn syrup, honey, or sugar cubes or table sugar (dissolved in water).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptom / effect | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist |
|------------------|-------------------------------------|--------------|---|
| | Only if severe | In all cases | |
| | | | |

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| | | Talk with your doctor or pharmacist | | |
|-----------------|--|-------------------------------------|---|---|
| Common | Low blood sugar level (hypoglycemia) The usual signs are : anxious feeling, drowsiness, chills, cold sweats, confusion, cool pale skin, difficulty in concentration, excessive hunger, fast heartbeat, headache, nausea, nervousness, shakiness, unsteady walk, unusual tiredness or weakness | | √ | |
| Uncommon | Unexplained fever chills or sore throat. Unusual bleeding or bruising. Yellowing of skin or eyes, dark-coloured urine or light-coloured bowel movements. Skin rash or hives. Oedema, swelling of the legs or unexpected weight gain. | | √ | √ |

This is not a complete list of side effects. For any unexpected effects while taking GLICLAZIDE MR, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of reach or sight of children.

Store at room temperature (15°C - 25°C). Protect from humidity.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form**

and:

- **Fax toll-free to 1-866-678-6789, or**
- **Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, ON K1A 0K9**

**Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at:
www.healthcanada.gc.ca/medeffect**

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, AA Pharma Inc., at 1-877-998-9097.

This leaflet was prepared by AA Pharma Inc.

Last revised: June 25, 2010