PRODUCT MONOGRAPH

PrRAN™-GLICLAZIDE MR

Gliclazide

Modified-Release Tablets
30 mg

Modified-Release Breakable Tablets
60 mg

Hypoglycemic sulfonylurea - Oral antidiabetic agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Modified-release tablet 30 mg Modified-release breakable tablet 60 mg	hypromellose, lactose monohydrate, magnesium stearate, sodium citrate and starch pregelatinised.

INDICATIONS AND CLINICAL USE

RAN-GLICLAZIDE MR(gliclazide) 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):
No significant differences in efficacy and tolerance were observed between patients over 65 years of age and younger patients, however greater sensitivity of some older individuals cannot be ruled out (see WARNINGS AND PRECAUTIONS — Special Population, and DOSAGEAND ADMINISTRATION).

Pediatrics (< 18 years of age):
Safety and effectiveness of gliclazide modified release tablets in children have not been established. RAN-GLICLAZIDE MR is therefore not recommended for use in children and adolescents.

CONTRAINDICATIONS

RAN-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 (Type 1) 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 hepatic impairment (see WARNINGS AND PRECAUTIONS).
- In the presence of severe renal impairment (see WARNINGS AND PRECAUTIONS).
- Treatmentwithmiconazole via systemicrouteororomucosalgel(seeDRUGINTERACTIONS).
- Pregnancy and lactation (see WARNINGS AND PRECAUTIONS — Special Populations, Pregnant Women and Nursing Women).

WARNINGS AND PRECAUTIONS

General

Use of RAN-GLICLAZIDE MR 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.

RAN-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 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 benecessary and glucose administration may need to be continued for several days.

Hypoglycemiamay be difficult to recognize in elderly patients and in patients receiving beta-blockers.

Possible other symptoms of hypoglycaemia 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 hospitalisation are required.

Other factors which increase the risk of hypoglycemia are: overdose of gliclazidemodified release tablets, 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 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-linetreatment. 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 modified release tablets is detected, the drug should be discontinued.

In patients stabilized on gliclazide therapy, loss of blood sugar control may occur in cases of acute intercurrent disease such as a fever and serious infection, or in stressful situations such as trauma or surgery, or if used concomitantly with herbs such as St. John's Wort *(Hypericum perforatum)* preparations or any treatment that may interact with gliclazide metabolism (see DRUG INTERACTIONS & Drug-Herb Interactions). Under these conditions, discontinuation

of gliclazidemodified release tabletsand administration of insulin should be considered.

Dysglycaemia

Fluoroquinolones should be used with caution in patients receiving gliclazidemodified release tablets.Hypoglycaemia and hyperglycaemia have been reported in diabetic patientsreceiving concomitant treatment with fluoroquinolones, especially in elderly patients. Careful monitoring of blood glucose is recommended in all patients taking gliclazidemodified release tablets and a fluoroquinolone concomitantly.

Hematologic

Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD)-deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since gliclazidemodified release tabletsbelongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non- sulfonylurea alternative should be considered.

Hepatic/Biliary/Pancreatic

The metabolism and excretion of sulfonylureas including gliclazidemodified release tabletsmay be slowed in patients with impaired hepatic function. Isolated cases of impairment of liver function with cholestasis and jaundice, and hepatitis which can regress after withdrawal of the drug or may lead to life-threatening liver failure have been observed. Discontinue treatment if cholestatic jaundice appears. Therefore, gliclazidemodified release tablet is contraindicated in patients with severe hepatic impairment (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS — 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 modified release tabletsand administration of insulin should be considered (see WARNINGS AND PRECAUTIONS — Endocrine and Metabolism,Poor blood glucose control).

Renal

The metabolism and excretion of sulfonylureas including gliclazidemodified release tabletsmay 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. Therefore, gliclazidemodified release tablet is contraindicated in patients with severe renal impairment (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS — Monitoring and Laboratory Tests).

Sensitivity/Resistance

Due to the presence of lactose in RAN-GLICLAZIDE MR, patients with hereditary problems of galactose intolerance, glucose-galactose malabsorption or the Lapp lactose deficiency should not take RAN-GLICLAZIDE MR.

Skin

Serious skin and hypersensitivity reactions including rash, pruritus, urticaria, angioedema,

erythema, maculopapular rashes, bullous reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis) and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported.

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:
Gliclazide modified release tablet is contraindicated in breast-feeding mothers. Some sulfonylurea drugs are excreted in human milk although it is not known whether gliclazide is one of them. Because the potential for hypoglycemia in nursing infants may exist, the product is contraindicated in breast-feeding mothers (see CONTRAINDICATIONS).

Pediatrics (< 18 years of age):
Safety and effectiveness of gliclazide modified release tablets in children have not been established. RAN-GLICLAZIDE MR is therefore not recommended for use in children and adolescents.

Geriatrics (≥ 65 years of age):
Efficacy and tolerance of gliclazide modified release tablets, prescribed using the same therapeutic regimen in subjects over 65 years, has been confirmed in clinical trials, however greater sensitivity of some older individuals cannot be ruled out.

Severe hypoglycemia can be induced by all sulfonylurea drugs. Elderly subjects are particularly susceptible.

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 gliclazide modified release tabletstreatment may be affected by fever, infection, surgical interventionor when used concomitantly with St. John's Wort *(Hypericum perforatum)* preparations. Close 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 mild to moderately impaired hepatic function.

In patients with mild to moderately impaired renal function, renal function should be assessed periodically. Blood glucose and glycated hemoglobin levels should be regularly monitored in all patients.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Gliclazide 30 mg modified release tablets has 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 most frequent adverse drug reactions are hypoglycaemia and gastrointestinal disturbances (including abdominal pain, nausea, vomiting, dyspepsia, diarrhea, constipation).

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 impairment, 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 30 mg modified release tablets(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 30 mg modified release tabletsgroup (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 30 mg modified release tabletsgroup (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 30 mg modified release

tabletswere 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 Table 1. The most frequent adverse events were unspecific of the disease as respiratory infections or back pain.

Table 1 – Adverse events reported in ≥1% of type 2 diabetic patients in long-term controlled studies with Gliclazide 30 mg modified-release *vs.* Gliclazide 80 mg

	Gliclazide (modified-release) 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

Table 1 – Adverse events reported in ≥1% of type 2 diabetic patients in long-term controlled studies with Gliclazide 30 mg modified-release *vs.* Gliclazide 80 mg

	Gliclazide (modified-release) 30 mg (n= 728) %	Gliclazide 80 mg tablets (n=734) %
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		
Hypoglycemia	11.6	11.1
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 pattern 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 30 mg modified release tabletsduring 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.

Gastrointestinal: 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 test abnormalities other than those already reported with gliclazide 80 mg tablets have been observed during controlled clinical trials performed on gliclazide 30 mg modified release tablets.

Post-Market Adverse Drug Reactions

In post-marketing experience with gliclazide modified release tablets, gastrointestinal disturbance, including abdominal pain, nausea, vomiting, dyspepsia, diarrhea and constipation have been 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 drug rash with eosinophilia and systemic symptoms (DRESS) have been 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).

The following adverse events have also been observed with gliclazide: cases of erythrocytopenia, agranulocytosis, hemolytic anemia, allergic vasculitis, hyponatremia, and elevated liver enzyme levels (AST, ALT, alkaline phosphatase); isolated cases of impairment of liver function with cholestasis and jaundice which can regress after withdrawal of the drug or may lead to life-threatening liver failure. Discontinue treatment if cholestatic jaundice appears.

DRUG INTERACTIONS

Serious Drug Interactions
The concomitantuse of miconazoleandgliclazideiscontraindicated(see CONTRAINDICATIONS).

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, angiotensin converting enzyme inhibitors and clarithromycin. In addition, while not approved for use with other antidiabetic agents, hypoglycaemia is potentiated when gliclazide is used in combination with other antidiabetic agents.

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

Table 2 – Established or Potential Drug-Drug Interactions

Gliclazide	Reference	Effect	Clinical Comment
Miconazole (systemic route, oromucosal gel)	**C**	Increases the risk ofhypoglycaemia	Contra-indicated combination. Increases the hypoglycaemic effect with possible onset of hypoglycaemic symptoms, or even coma.
Phenylbutazone (systemic route)	**C**	Increases the risk of hypoglycaemia	Combination is not recommended. 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 ofhypoglycaemia	Combinations requiring precautions for use. Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur.
Beta-blockers	**C**	Increases the risk ofhypoglycaemia	Combinations requiring precautions for use. Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur.
Fluconazole	**C**	Increases the risk ofhypoglycaemia	Combinations requiring precautions for use. Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur.
Angiotensin converting enzyme inhibitors	**C**	Increases the risk ofhypoglycaemia	Combinations requiring precautions for use. Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur.
H2-receptor antagonists	**C**	Increases the risk ofhypoglycaemia	Combinations requiring precautions for use. Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur.
MAOIs	**C**	Increases the risk ofhypoglycaemia	Combinations requiring precautions for use. Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur.
Sulfonamides	**C**	Increases the risk ofhypoglycaemia	Combinations requiring precautions for use. Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur.
Nonsteroidal anti-inflammatory agents	**C**	Increases the risk ofhypoglycaemia	Combinations requiring precautions for use. Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur.

Gliclazide	Reference	Effect	Clinical Comment
Clarithromycin	**T**	Increases the risk ofhypoglycaemia	Combinations requiring precautions for use. May potentiate the hypoglycemic action of sulfonylurea agents.
Danazol	**C**	Causes an increase in blood glucose levels	Combination is not recommended because of 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.
Chlorpromazine (neuroleptic agent)	**C**	Causes an increase in blood glucose levels	Combination requiring precautions during use. 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 tetracosactide	**C**	Causes an increase in blood glucose levels	Combination requiring precautions during use. 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	Combination requiring precautions during use. 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**	Potentiation of anticoagulation	Combination which must be taken into account.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 hypoglycaemia	Intolerance to alcohol (disulfiram-like reaction: flushing, sensation of warmth, giddiness, nausea and occasionally tachycardia) may occur in patients treated with sulfonylurea.
Fluoroquinolones	**T**	Increases the risk of dysglycaemia	Combinations requiring precautions for use. Warn the patient and emphasise the importance of monitoring blood glucose

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

Drug-Food Interactions

There are no established drug-food interactions.

Drug-Herb Interactions

St. John's Wort
Pharmacodynamic interactions between gliclazide and the herbal remedy St. John's Wort may occur and may lead to hyperglycemia or loss of blood glucose control.

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 increasedrisk of hypoglycemia if a meal is taken late, if an inadequate amount of food is consumed or ifthe 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 gliclazidemodified release tabletscan have effects on ability to drive and use machines. Patients should be made aware of the symptoms of hypoglycaemia 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 RAN-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 RAN-GLICLAZIDE MR may vary from 30 to 120 mg once daily (i.e., one half tablet to 2 tablets of RAN-GLICLAZIDE MR 60 mg, or 1 to 4 tablets of RAN-GLICLAZIDE MR 30 mg).

Recommended Dose and Dosage Adjustment

The recommended starting dose of RAN-GLICLAZIDE MR is 30 mg daily, i.e. one half tablet of RAN-GLICLAZIDE MR60 mg or one tablet of RAN-GLICLAZIDE MR 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 30 mg and 90 mg, or even 120 mg. 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.

Missed Dose

If a dose is forgotten, the patient should be advised to skip the missed dose and take his or her usual dose at the regular time the next day. The dose taken on the next day should not be increased to account for the missed dose.

Administration

It is recommended that the medication be taken at breakfast time. The 30 mg tablets cannot be split in half and should be swallowed whole.The 60 mg tablets can be halved. Both the 30 mg and 60 mg tabletsmust not be chewed or crushed.

- Previously untreated patients should commence with a dose of 30 mg i.e. one half tablet of RAN-GLICLAZIDE MR 60 mg and will benefit from dose adjustment until the appropriate dose is reached.
- One RAN-GLICLAZIDE MR 60 mg tablet is equivalent to two RAN-GLICLAZIDE MR 30 mg tablets. The breakability of the RAN-GLICLAZIDE MR(modified-release) 60 mg tablet allows the use of a dose of 30 mg as a half tablet and of 90 mg as one and a half tablets.
- RAN-GLICLAZIDE MRcan 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.

Geriatrics

No significant differences in efficacy and tolerance were observed between patients over 65 years of age and younger patients, however greater sensitivity of some older individuals cannot be ruled out. Patients over 65 years of age should be started with gliclazide 30 mg modified release tabletsi.e. one half tablet of RAN-GLICLAZIDE MR 60 mgwith dosage adjustments being made cautiously.

Hepatic or Renal Impairment

Patients with renal or hepatic impairment should be started with gliclazide 30 mg modified release tabletsi.e. one half tablet of RAN-GLICLAZIDE MR 60 mg with dosage adjustments being made cautiously (see WARNINGS AND PRECAUTIONS —Hypoglycemic reactions).

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 gliclazidemodified release tabletstherapy after cessation of insulin.

If a change from insulin to gliclazide modified release tablet 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.

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 arepossible and must be treated as a medical emergency, requiring immediate hospitalization.

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

For management of a suspected drug overdose contact your regional Poison Control Centerimmediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Gliclazide modified release tablet is a hypoglycemic agent of the sulfonylurea group. The hypoglycemic action of gliclazide modified release tablet 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 theseeffects 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 of 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 by2 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

Absorption:

Gliclazide is slowly and completely absorbed from the gastro-intestinal tract (mean absolute bioavailability of 97%).

After administration, 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. 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. Linear kinetics were observed with gliclazide 30 mg modified release tabletsin thedose range up to 120 mg.

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

A single daily dose of gliclazide 30 mg modified release tabletsmaintains effective gliclazide plasma concentrations over 24 hours.

Metabolism:
Although more than 90% of unchanged gliclazide is found in plasma following oral administration, this is extensively metabolized with little of the unchanged compound (<1%) found in urine. Six principal metabolites have been identified in urine, essentially oxidized and hydroxylated derivatives, and two glucuronoconjugates. No active metabolites have been detected in plasma.

Excretion:
Gliclazide metabolites and conjugates are primarily (60-70%) eliminated via the urine, with about 10 to 20% elimination via feces.
The mean elimination half life is 16 h (range 12-20 h).

Special Populations and Conditions

Pediatrics: Safety and effectiveness of gliclazide modified release tablets in children have not been established. RAN-GLICLAZIDE MR is therefore not recommended for use in children and adolescents.

Geriatrics: No clinically significant modifications in the pharmacokinetic parameters have been observed in elderly patients.

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

STORAGE AND STABILITY
Store at a temperature 15°C-30°C. Protected from moisture and heat.
Keep out of reach and sight of children and pets.
Unused medication should not be disposed of down the drain or in household garbage.

SPECIAL HANDLING INSTRUCTIONS
No special requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage form:

RAN-GLICLAZIDE MR 30 mg are white to off-white oblong tablets, engraved with "**Z**" on one side and plain on the other side. Each tablet contains 30 mg of gliclazide.

RAN-GLICLAZIDE MR 60 mg are white to off-white oblong tablets, scored on both sides, engraved with "**Z"**and "**I**" on one side and plain on the other side. Each tablet contains 60 mg of gliclazide.

Composition:
Each tablet of RAN-GLICLAZIDE MR 30 mg contains:
Drug substance: 30 mg gliclazide
Excipients: hypromellose, lactose monohydrate,magnesium stearate, sodium citrate and starch pregelatinised.

Each tablet of RAN-GLICLAZIDE MR 60 mg contains:
Drug substance: 60 mg gliclazide
Excipients: hypromellose, lactose monohydrate, magnesium stearate, sodium citrate and starch pregelatinised.

Packaging:

RAN-GLICLAZIDE MR 30 mg is available in blister pack of 10s and 18s and bottles of 100s.

RAN-GLICLAZIDE MR 60 mg is supplied incartons of 60s (6 x 10 blister strips)and bottles of 100s.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

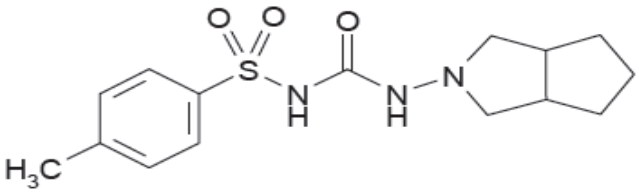
Proper name: gliclazide

Chemical name: 1-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-3-[(4-methylphenyl)sulphonyl]urea (European Pharmacopoeia)

Molecular formula: $C_{15}H_{21}N_3O_3S$

Molecular mass: 323.4 g/mol

Structural formula:



Physicochemical properties:

Appearance: white or almost white powder.

Solubility: practically insoluble in water
freely soluble in methylene chloride
sparingly soluble in acetone
slightly soluble in ethanol 96%.

Acid function pKa: 5.8

Overall distribution coefficient of gliclazide between water and octanol at pH 7.4 (Log $D_{pH\ 7.4}$) is 0.4

Melting point: 164°C

CLINICAL TRIALS

Comparative Bioavailability Studies

FASTING CONDITION:

A balanced, randomized, blinded, two treatment, two sequence, two period, single dose crossover bioequivalencestudy comparing test product RAN-GLICLAZIDE MR Tablets 30 mg [Ranbaxy Pharmaceuticals Canada Inc.] with reference product PrDIAMICRON® MR 30 mg (Gliclazide 30 mg Modified release tablets)manufactured by SERVIER CANADA INC. Laval, Quebec H7V 4A7, CANADA in healthy, adult, human subjects under fasting condition. The results from measured data in 27 subjects are summarised in the following table.

Table 3 -SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Gliclazide (1 x 30 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means#	90%Confidence Interval
AUC_{0-t} (ng.hr/mL)	23898.1404 27498.6249 (39.24)	24727.7117 24970.2854(33.93)	101.55	97.69 - 105.56
$AUC_{0-\infty}$ (ng.hr/mL)	25335.0914 25593.5788 (35.45)	23517.6325 26529.4000 (37.22)	102.11	97.66 - 106.77
C_{max} (ng /mL)	1023.740 1055.304 (24.47)	962.922 990.633 (23.89)	106.12	99.97$ - 112.66$
T_{max}^ (h)	8.500 (6.500– 12.000)	9.000 (7.000– 12.000)		
$T_{1/2}$~(h)	20.5549 (42.06)	20.1680 (33.50)		

* RAN-GLICLAZIDE 30 mg MR tablets (Ranbaxy Pharmaceuticals Canada Inc)
† DIAMICRON® MR tablet 30 mg (Servier Canada Inc., Canada) were purchased in Canada.
^ Expressed as Median (Range) only
~ Expressed as Arithmetic Mean (CV%) only
# Calculation based on least squares estimate
$: For Information Purpose only.

FED CONDITION:

A balanced, randomized, blinded, two treatment, two sequence, two period, single dose crossover bioequivalence study comparing test product RAN-GLICLAZIDE MR Tablets 30 mg [Ranbaxy Pharmaceuticals Canada Inc.] with reference product [Pr]DIAMICRON® MR 30 mg (Gliclazide 30 mg Modified release tablets)manufactured by SERVIER CANADA INC. Laval, Quebec H7V 4A7, CANADA in healthy, adult, human subjects under fed condition. The results from measured data in 24 subjects are summarised in the following table.

Table 4 - SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Gliclazide (1 x 30 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means#	90%Confidence Interval
AUC_{0-t} (ng.hr/mL)	26256.4321 28636.1708 (38.95)	26991.2959 29218.1179 (37.03)	97.27	93.65- 101.03
$AUC_{0-\infty}$ (ng.hr/mL)	27879.7775 30883.1369 (43.30)	28494.7946 31260.5982 (41.08)	97.84	94.03- 101.80
C_{max} (ng /mL)	1100.375 1129.931 (22.07)	1180.729 1194.498 (15.05)	93.19	87.29$- 99.49$
T_{max}^ (h)	9.000 (4.000– 16.017)	7.250 (5.000– 11.000)		
$T_{1/2}$~(h)	20.7143 (36.77)	20.1385 (34.65)		

* RAN-GLICLAZIDE 30 mg tablets (Ranbaxy Pharmaceuticals Canada Inc)
† DIAMICRON® MR tablet 30 mg (Servier Canada Inc., Canada) were purchased in Canada.
^ Expressed as Median (Range) only
~ Expressed as Arithmetic Mean (CV%) only
# Calculation based on least squares estimate
$: For Information Purpose only.

FASTING CONDITION:

A blinded, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of 1 x 60 mg RAN-GLICLAZIDE MR (Gliclazide) modified release tablets [Ranbaxy Pharmaceutical Canada Inc.]with 1 x 60 mgDIAMICRON® MR (Gliclazide) tablets[Servier Canada Inc.] was conducted in 26 healthy, adult, human subjects under fasting condition.

Table 5 - SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Gliclazide (1 x 60 mg) From measured data Least Square Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*(T)	Reference†(R)	% Ratio of LS Geometric Means[#]	90% Confidence Interval[#]
AUC_{0-t} (ng.hr/mL)	52538.2 58273.8 (44.7)	50495.2 56307.5 (42.6)	104.0	92.2– 117.4
$AUC_{0-\infty}$ (ng.hr/mL)	53694.3 57783.3 (41.9)	51700.4 57934.4 (41.7)	103.9	91.0- 118.5
C_{max} (ng /mL)	1980.2 2133.7 (39.0)	1949.4 2085.4 (30.2)	101.6	88.3- 116.9
T_{max}^(h)	11.0 (6.5- 24.0)	9.5 (5.0- 16.0)	-	-
$T_{1/2}$~(h)	21.3 (28.8)	22.4 (30.6)	-	-

* RAN-GLICLAZIDE MR(Gliclazide) 60 mg tablets(Ranbaxy Pharmaceuticals Canada Inc.).
† DIAMICRON® MR (Gliclazide) tablet 60 mg (Servier Canada Inc.) were purchased in Canada.
^ Expressed as Median (Range) only
~ Expressed as Arithmetic Mean (CV%) only
[#]Calculation based on least squares estimate

FED CONDITION:

A blinded, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of 1 x 60 mg RAN-GLICLAZIDE MR (Gliclazide) modified release tablets [Ranbaxy Pharmaceutical Canada Inc.]with 1 x 60 mgDIAMICRON® MR (Gliclazide) tablets[Servier Canada Inc.] was conducted in 20 healthy, adult, human subjects under fed condition.

Table 6 - SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Gliclazide (1 x 60 mg) From measured data Least Square Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*(T)	Reference†(R)	% Ratio of LS Geometric Means[#]	90% Confidence Interval[#]
AUC_{0-t} (ng.hr/mL)	68490.8 73699.3 (44.7)	61487.4 67297.3 (44.2)	111.4	101.3 - 122.5
$AUC_{0-\infty}$ (ng.hr/mL)	69851.9 74994.0 (42.6)	61796.7 67255.7 (38.8)	113.0	101.9 - 125.4
C_{max} (ng/mL)	2749.2 2900.8 (29.1)	2384.8 2545.2 (31.5)	115.3	102.3[$] - 129.9[$]
T_{max}^ (h)	9.5 (6.5- 20.0)	11.0 (6.5- 16.0)	-	-
$T_{1/2}$~(h)	23.5 (34.9)	22.1 (28.5)	-	-

***** RAN-GLICLAZIDE MR (Gliclazide) 60 mg tablets(Ranbaxy Pharmaceuticals Canada Inc.).
† DIAMICRON® MR (Gliclazide) tablet 60 mg (Servier Canada Inc.) were purchased in Canada.
^ Expressed as Median (Range) only
~ Expressed as Arithmetic Mean (CV%) only
[#]Calculation based on least squares estimate
[$] For Information Purpose only.

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

The first study was a phase II, multicenter, 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 (HbA1c) 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 30 mg compared to the gliclazide 80 mg immediate release formulation. A total of 664 patients were randomized in two parallel groups, one assigned to gliclazide 80 mg (336 patients) and one to gliclazide MR 30 mg (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 30 mg 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 30 mg is at least as effective as gliclazide 80 mg in controlling HbA1c 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 immediate release 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.

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 main characteristics are shown in the table below.

Table 7 - BLOOD KINETICS OF GLICLAZIDE (PO) IN DIFFERENT SPECIES (single doses)

Species	Number of animals Doses (mg/kg)	Absorption T ½ (h)	Time to 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]	-

PO: per os
[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 intensively 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 insulinotropic 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

Table 8

Species	Mean Weight	Number of animals per lot	DL 50 (mg/kg)	
Mouse CD-SPF	25 g	10 M 10 F	> 3 000	
Mouse ICR-HAN	20 g	10 M 10 F	> 4 000	
Rat SD-SPF	250 g	10 M	3733 (5200 / 2679)	
		10 F	3407 (5467 / 2123)	
Rat CFY	110 g	6 M 6 F	> 4 000	
Tricolor Guinea Pig	240 g		48 hours	10 days
		4 M	1732 (1999 / 1501)	1599 (2016 / 1269)
		4 F	2244 (2509 / 1944)	2068 (2553 / 1675)
Beagle dog	7 kg	3 M 3 F	> 3000	

The LD 50 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. 200 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 behavior, 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 occured as a result of technical problems. All other animals showed normal behavior 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.

In a six-month rat study carried out in Japan with higher doses (0, 50, 100, 200, 400 and 800 mg/kg/day) females exhibited greater systemic toxicity when compared with males, suggesting that females may be more sensitive 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 0, 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 behavior 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, 50,250 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 starting from mating and throughout gestation had no effect on fertilization, gestation, mean number of foetuses or incidence of foetal 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 foetal resorptions, percentage of abortion nor the mean number of foetuses 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 renallesions 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. Foetal resorption,

placental haemorrhage and foetal atrophy rates were unaffected. The genital tract of treated parents showed no abnormality imputable to treatment. No embryotoxic effect was seen on foetuses 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 wereprepared 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 thisimpurity:

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 did 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.

REFERENCES

1. ALMER L.O."Effect of chlorpropamide and gliclazide on plasminogen activator activity in vascular walls in patients with maturity onset diabetes", Thromb Res 1984; 35(1):19-25

2. BAK J.F., SCHMITZ O., SORENSEN N.S., et al "Postreceptor effects of sulfonylurea on skeletal muscle glycogen synthase activity in type II diabetic patients", Diabetes 1989;38(11):1343-50

3. BARNETT A.H. "Pathogenesis of diabetic microangiopathy: an overview", Am J Med 1991;90(6A):67S- 73S

4. BODANSKY H.J., MEDBACK S., CUDWORTH A.G. et al. "Long term improvement in insulin response with gliclazide treatment", Diabete Metab 1982;8(4):319-22

5. BOUSKELA E., CYRINO F.Z., CONDE C.M. et al. "Microvascular permeability with sulfonylureas in normal and diabetic hamsters", Metabolism 1997; 46(12 Suppl 1):26-30

6. CHAN T.K., CHAN V., TENG C.S., YEUNG R.T.T., «Effets du gliclazide et du glibenclamide sur les fonctions plaquettaires, la fibrinolyse et l'équilibre glycémique chez des diabétiques présentant une rétinopathie», Sem Hop Paris 1982;58(19):1197-1200

7. COLLIER A., WATSON H.H., PATRICK A.W., et al «Effect of glycemic control, metformin and gliclazide on platelet density and aggregability in recently diagnosed type 2 (non-insulin-dependent) diabetic patients», Diabete Metab 1989; 15(6):420-5

8. DESFAITS A.C., SERRI O., RENIER G. "Gliclazide decreases cell-mediated low-density lipoprotein (LDL) oxidation and reduces monocyte adhesion to endothelial cells induced by oxidatively modified LDL" Metabolism 1997; 46(10):1150-6

9. DESFAITS A.C., SERRI O., RENIER G."Gliclazide reduces the induction of human monocyte adhesion to endothelial cells by glycated albumin", Diabetes, Obesity & Metabolism 1999, Mar; 1(2):113-20.

10. DUHAULT J., REGNAULT F., BOULANGER M. et al "Prevention of experimental obstructions in the retinal microcirculation", Ophtalmologica 1975;170:345-352

11. FLORKOWSKI C.M., RICHARDSON M.R., LE GUEN C. et al. "Effect of gliclazide on thromboxane B2, parameters of haemostasis, fluorescent IgG and lipid peroxides in non-insulin dependent diabetes mellitus", Diabetes Res 1988; 9(2):87-90

12. FU Z.Z., YAN T., CHEN Y.J. et al. "Thromboxane/prostacyclin balance in type II diabetes: gliclazide effects", Metabolism 1992; 41(5 Suppl 1):33- 5

13. GAMSTEDT A., FAGERBERG S.E. «Long-term metabolic effects of gliclazide in NIDDM», FADL Publish 1987; 16-19

14. GOLAY A., BROQUET C., CHABOT V. et al. «Effets métaboliques du gliclazide chez le diabétique de type II. Etude par calorimétrie indirecte», Schweiz Med Wochenschr 1984;114(8):261-264

15. GRAM J., JESPERSEN J., KOLD A. «Effects of an oral antidiabetic drug on the fibrinolytic system of blood in insulin-treated diabetic patients», Metabolism 1988; 37:937-943

16. GRAM J., KOLD A., JESPERSEN J "Rise of plasma t-PA fibrinolytic activity in a group of maturity onset diabetipatients shifted from a first generation (tolbutamide) to a second generation sulphonylurea (gliclazide)" , J Intern Med 1989; 225(4):241-7

17. GRAM J., JESPERSEN J., DOOIJEWAARD G., et al "The effect of gliclazide on plasma urokinase-related fibrinolysis. The results from an exploratory study", Fibrinolysis 1994;8(Suppl 2):60-62

18. HARROWER A. "Comparison of diabetic control in type 2 (non-insulin dependent) diabetic patients treated with different sulphonylureas", Curr Med Res Opin 1985;9:676-680

19. HOICH R.I., NG F.M. "Insulin-potentiating action of gliclazide (Diamicron) ", Pharmacol Res Commun 1986; 18(5):419-430

20. HOSKER J.P., RUDENSKI A.S., BURNETT M.A., et al "Similar reduction of first- and second- phase B-cell responses at three different glucose levels in type II diabetes and the effect of gliclazide therapy", Metabolism 1989;38(8):767-72

21. INGS R.M.J., CAMPBELL B., GORDON B.H. et al "The effect of renal disease on the pharmacokinetics of gliclazide in diabetic patients", Br J Clin Pharmacol 1986; 21(5):572-573

22. JENNINGS P.E., SCOTT N.A., SANIABADI A.R. et al. "Effects of gliclazide on platelet reactivity and free radicals in type II diabetic patients: clinical assessment", Metabolism 1992; 41(5 Suppl 1):36-9

23. JOHNSON A.B., ARGYRAKI M., THOW J.C. et al. "The effect of sulphonylurea therapy on skeletal muscle glycogen synthase activity and insulin secretion in newly presenting type 2 (non-insulin-dependent) diabetic patients", Diabet Med 1991; 8(3):243-53

24. KILO C., DUDLEY J., KALB E. "Evaluation of safety and efficacy of gliclazide in non-insulin-dependent diabetic patients", Bull Int Diabete Fed 1987; 32(1):27-29

25. KUWASHIMA J. et al. "Inhibition by gliclazide of platelet adhesiveness and aggregation in the rabbit made diabetic by alloxan", Yakugaku Zasshi 1979; 99(1):59-64

26. MARCHAND D. et al. "The hypoglycemic effect of a sulfonylurea (gliclazide) in moderate type II diabetes and glucose intolerance is not accompanied by changes in insulin action

and insulin binding to erythrocytes", Molecular Physiology 1983;4:83-93

27. MARQUIE G., HADJIISKY P., ARNAUD O. et al. "Development of macroangiopathy in sand rats (Psammomys obesus), an animal model of non-insulin-dependent diabetes mellitus: effect of gliclazide", Am J Med 1991; 90(6A):55S-61S

28. O'BRIEN R.C., LUO M. "The effects of gliclazide and other sulfonylureas on low-density lipoprotein oxidation in vitro", Metabolism 1997; 46(12 Suppl 1):22-5

29. PAGANO P.J., GRISWOLD M.C., RAVEL D. et al. "Vascular action of the hypoglycaemic agent gliclazide in diabetic rabbits", Diabetologia 1998; 41:9-15

30. PHENEKOS C., SIAFAKA-KAPADAI A., TRAPALI M., et al "Effect of gliclazide on platelet-activating factor-induced platelet aggregation in patients with non-insulin-dependent diabetes mellitus", Metabolism 1992; 41(5 Suppl 1):30-2

31. QUATRARO A., CONSOLI G., CERIELLO A. et al. "Combined insulin and sulfonylurea therapy in non-insulin-dependent diabetics with secondary failure to oral drugs: a one-year follow-up", Diabete Metab 1986; 12:315-318

32. REGNAULT F. "Gliclazide in the treatment of diabetic retinopathy", Adv Exp Med Biol 1979; 119:443- 448

33. RENIER G., DESFAITS A.C., SERRI O. "Gliclazide decreases low-density lipoprotein oxidation and monocyte adhesion to the endothelium", Metabolism 1999, in press

34. RICCIO A., LISATO G., DE KREUTZENBERG S.V. et al. "Gliclazide potentiates suppression of hepatic glucose production in non-insulin-dependent diabetic patients", Metabolism 1996; 45(10):1196-202

35. SCOTT N.A., JENNINGS P.E., BROWN J., et al "Gliclazide: a general free radical scavenger", Eur J Pharmacol 1991; 208(2):175-7

36. SHIMABUKURO M., NAGAMINE F., MURAKAMIK. et al. "Chronic gliclazide treatment affects basal and post-ischemic cardiac function in diabetic rats", Gen Pharmac 1994; 25(4):697-704

37. TURNER R.C., HOSKER J.P., RUDENSKI A.S. et al. "Similar reduction of first and second phase B-cell responses at three different glucose levels in type II diabetes, and the effect of gliclazide therapy", Metabolism 1989;38(5):107-110

38. VESTERGAARD H., WEINREB J.E., ROSEN A.S. et al."Sulfonylurea therapy improves glucose disposal without changing skeletal muscle GLUT4 levels in non insulin-dependent diabetes mellitus subjects: a longitudinal study"J Clin Endocrinol Metab 1995; 80(1):270-5

39. WAJCHENBERG B.J., SANTOMARUO A.T., CHEREM J.J., et al "Effect of gliclazide on non-insulin dependent diabetes mellitus", Adv Exp Med Biol 1988

40. WAJCHENBERG B.L., SANTOMAURO A.T., GIANNELLA-NETO D., et al "Short - and long-termgliclazide effects on pancreatic islet cell function and hepatic insulin extraction in non-insulin-dependent diabetes mellitus", Diabetes Res Clin Pract 1992;17(2):89-97

41. WAJCHENBERG B.L., SANTOMAURO A.T., PORRELLI N. "Effect of a sulfonylurea (gliclazide) treatment on insulin sensitivity and glucose-mediated glucose disposal in patients with non-insulin-dependent diabetes mellitus (NIDDM)", Diabetes Res Clin Pract 1993;20(2):147-54

42. WARD G., HARRISON L.C., PROIETTO J., et al "Gliclazide therapy is associated with potentiation of postbinding insulin action in obese, non-insulin-dependent diabetic subjects", Diabetes 1985; 34(3):241-5

43. "Clinical Practice Guidelines for the Management of Diabetes in Canada", CMAJ 1998; 159(8 Suppl)

44. Product Monograph of PrDIAMICRON® MR(Gliclazide) Modified-Release Tablets 30 mg and Modified-Release Breakable Tablets 60 mg, SERVIER CANADA Inc., Date of Revision October 20, 2016, Submission Control No. 197557.

PART III: CONSUMER INFORMATION

PrRAN™-GLICLAZIDE MR

Gliclazide
Modified-Release Tablets
30 mg
Modified-Release Breakable Tablets
60 mg

This leaflet is part III of a three-part "Product Monograph" published when RAN-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 RAN-GLICLAZIDE MR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

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

What it does:

RAN-GLICLAZIDE MR belongs to the family of hypoglycemic(antidiabetic) drugs and part of a sub family of medicines calledsulfonylureas. It helps improve insulin secretion in the body.

When it should not be used:

RAN-GLICLAZIDE MR is contraindicated (must not be taken):
- if you are allergic or hypersensitive to gliclazide, othersulfonylureas, sulfonamides, or to any of the ingredients ofthese products,
- if you have unstable and/or insulin-dependent diabetesmellitus, juvenile diabetes (type I diabetes), diabeticketoacidosis, diabetes pre-coma and coma,
- if you have a serious infection, trauma or surgery,
- if you have severe liver problems,
- if you have severe kidney problems,
- if you receive treatment with miconazole,
- if you are pregnant and/or breast-feeding.

What the medicinal ingredient is:

Gliclazide.

What the nonmedicinal ingredients are:

RAN-GLICLAZIDE MR 30 mg tablets contain: hypromellose,lactose monohydrate, magnesium stearate, sodium citrate and starch pregelatinised.

RAN-GLICLAZIDE MR 60 mg tablets contain: hypromellose, lactose monohydrate, magnesium stearate,sodium citrate and starch pregelatinised.

What dosage forms it comes in:

RAN-GLICLAZIDE MR comes inmodified-release tablets of 30 mg andmodified-release breakable tablets of 60 mg.

WARNINGS AND PRECAUTIONS

RAN-GLICLAZIDE MR may cause low blood sugar (hypoglycemia).You should ask your doctor, pharmacist or diabetes educatorabout symptoms of low blood sugar and what to do if youexperience these symptoms. You should also test your bloodsugar as instructed by your doctor.

BEFORE you use RAN-GLICLAZIDE MR talk to your doctor orpharmacist if:
- you have or have had liver problems,
- you have or have had kidney problems,
- you are pregnant or planning to get pregnant,
- you are breast-feeding,
- you have a blood disease called G6PD-deficiency anemia,
- you have an intolerance to lactose.

Your blood sugar may get too high (hyperglycaemia) if youtake Saint John's Wort preparations or if you experience fever, infection, surgery or trauma (stress conditions).In such cases, contact your doctor as your medication may need tobe adjusted. Serious Skin Reactions (DRESS, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, hypersensitivity Syndrome): any combination of red itchy rash with blisters and peeling of the skin and /or of the lips, eyes, mouth, nasal passages or genitals. It often goes with fever, chills, headache, cough, body aches or joint pain. You may have less or dark urine, yellow skin or eyes. If you suspect these, you should stop taking the drug and talk with your doctor or pharmacist.

Low blood sugar and high blood sugar can occur when gliclazidemodified release tablets is prescribed at the same time as medicines belonging to a class of antibiotics called fluoroquinolones, especially if you are elderly. If you are taking these medications together, your doctor will remind you of the importance of monitoring your blood glucose.

RAN-GLICLAZIDE MR is not recommended for use in children under18 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. Thismay affect your ability to drive or to operate machinery.

INTERACTIONS WITH THIS MEDICATION

Serious Drug Interactions

RAN-GLICLAZIDE MR (gliclazide) should not be taken if you are also taking miconazole (an anti-fungal drug). See **"When it should not be used"** section of this leaflet.

Other drugs that may interact with RAN-GLICLAZIDE MR include:
- other antidiabetic agents
- antibiotics (sulphonamides/sulfa drugs, clarithromycin,

fluoroquinolones)
- anti-tuberculosis drugs
- anti-fungal drugs (fluconazole)
- non-steroidal anti-inflammatory drugs (NSAIDs)including phenylbutazone (used to treat inflammationand pain)
- cortiscosteroids (used to treat inflammation)
- salicylates (e.g. acetylsalicylic acid)
- angiotensin converting enzyme (ACE) inhibitors (used totreat high blood pressure and certain heart conditions)
- beta blockers (used to treat high blood pressure andcertain heart conditions)
- anticoagulant therapy (blood thinners), including warfarin
- diuretics (thiazides, furosemide) (used to treat high bloodpressure and certain heart conditions)
- fibrates, nicotinic acid (used to treat high levels of fats inthe blood)
- H_2-receptor antagonists (used to treat acidreflux/heartburn)
- monoamine oxidase inhibitors (used to treat depression)
- chlorpromazine (used to treat certain psychiatricconditions)
- probenecid (used to treat high levels of uric acid in theblood and gout)
- salbutamol, terbutaline (used to treat asthma) andritodrine
- barbiturates (sedatives, anti-seizure medications)
- oral contraceptives (estrogen plus progestogen, used forbirth control)
- danazol (used to treat breast cysts and endometriosis)
- alcohol.

Some of the drugs described above may lead to loss of blood sugarcontrol (high blood sugar), including diuretics, corticosteroids, oralcontraceptives, chlorpromazine, ritodrine, salbutamol, terbutaline,danazol and nicotinic acid.

Some herbs such as Saint John's Wort preparations may lead to high blood sugar and loss of blood sugar control.

Avoid drinking alcoholic beverages and taking medicinescontaining alcohol while you are taking RAN-GLICLAZIDE MR as thiscan lead to a drop in blood sugar (hypoglycaemia).

Tell your doctor if you have recently taken any of the medicineslisted above or any other medicines, including those obtainedwithout a prescription. Do not take other medicines unlessprescribed or approved by your doctor. Tell any health careprofessionals that you see that you are taking RAN-GLICLAZIDE MR.

PROPER USE OF THIS MEDICATION

Usual dose:
The recommended starting dose of RAN-GLICLAZIDE MR is 30 mgper day (a half tablet of RAN-GLICLAZIDE MR 60 mg or a tablet of RAN-GLICLAZIDE MR 30 mg), even in elderly patients (over 65 yearsold). The daily dose should not exceed 120 mg.

Take RAN-GLICLAZIDE MR once daily at breakfast. The 30 mg tablets cannot be split in half and should be swallowed whole with a glass of water. The 60 mg tablets can be halved.Do not crush or chew the tablets of either strength.

You should test your sugar level as directed by your physician tomake sure that your blood sugar is being controlled. Yourphysician should check your progress at regular visits, especiallyduring the first few weeks that you take this medicine.

Overdose:
If you think you have taken too much RAN-GLICLAZIDE MR, contact your health care professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of this medicine, skip the missed dose. Takeyour next dose at the regular time. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

RAN-GLICLAZIDE MR is associated with some side effects. It may,however, affect different people in different ways.

Common side effects reported during clinical trials withgliclazidemodified release tablets included:
- hypoglycemia (low blood sugar)
- hyperglycemia (high blood sugar)
- viral infection
- upper respiratory infection, runny nose, sore throat, cough
- back, muscle and joint pain
- headache
- high blood pressure
- angina (chest pain)
- leg swelling
- diarrhea, constipation, abdominal pain, nausea
- dizziness
- skin rash/itching
- depression

You should know that the usual signs of low blood sugar level(hypoglycemia) are: anxious feeling, drowsiness, dizziness,chills, cold sweats, confusion, cool pale skin, difficulty inconcentration, excessive hunger, fast heartbeat, headache,nausea, depression, nervousness, shakiness, unsteady walk,unusual tiredness or weakness. The following signs andsymptoms may also occur: clammy skin, anxiety, irregularheart beat, high blood pressure, chest pain or pressure, and/orshortness of breath (angina pectoris).Serious Skin Reactions (DRESS, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, hypersensitivity Syndrome): any combination of red itchy rash with blisters and peeling of the

skin and /or of the lips, eyes, mouth, nasal passages or genitals. It often goes with fever, chills, headache, cough, body aches or joint pain. You may have less or dark urine, yellow skin or eyes. If you suspect these, you should stop taking the drug and talk with your doctor or pharmacist.

If you recognize some of these signs of the drop in bloodsugar, immediately eat or drink something containing sugarand notify your doctor without delay. Good sources of sugarare: orange juice, corn syrup, honey, or sugar cubes or tablesugar (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 get immediate medical help
		Only if severe	In all cases	
Common	Low blood sugar level (hypoglycemia)		√	
	The usual signs are: anxious feeling,		√	
	Drowsiness		√	
	Chills		√	
	Cold sweats		√	
	Confusion		√	
	Cool pale skin		√	
	Difficulty inconcentration			
	Excessive hunger		√	
	Fast heartbeat		√	
	Headache		√	
	Nausea		√	
	Dizziness		√	
	Nervousness		√	
	Shakiness		√	
	Unsteady walk		√	
	Unusual tiredness or weakness		√	
Uncommon	Unexplained fever, chills or sore throat			√
	Yellowing of skinor eyes, dark-coloured urineor light-coloured bowel movements (e.g. jaundice)			√
	Skin rash, redness, itching or hives			√
	Oedema, swelling of the legs or unexpected weight gain		√	
	Chest pain or pressure, and/or shortness of breath			√
Very rare	Blood abnormalities with symptoms of sore throat, fever, mouth sore, unusual bleeding or bruising, low level of red blood cells (anemia)			√
	Allergic inflammation of blood vessels (vasculitis)			√
	Low sodium level in blood combined with symptoms of tiredness, weakness and confusion (hyponatraemia)			√
	Rapid swelling of tissues such as eyelids, face, lips, mouth, tongue or throat that may result in breathing difficulty (angioedema)			√
	Serious Skin Reactions (DRESS, Stevens-Johnson Syndrome,Toxic Epidermal Necrolysis, hypersensitivity Syndrome): any combination of red itchy rash with blisters and peeling of the skin and /or of the lips, eyes, mouth, nasal passages or genitals. It often goes with fever, chills, headache, cough, body aches or joint pain. You may have less or dark urine, yellow skin or eyes			√

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

HOW TO STORE IT

Keep out of reach or sight of children and pets.

RAN-GLICLAZIDE MR should be store at a temperature 15° C - 30° C. Protected from moisture and heat.

Medicines should not be disposed of down the drain or in household garbage. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php)for information on how to report on by mail or by fax; or
- Calling toll-free at1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects.The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor Ranbaxy Pharmaceuticals Canada Inc. at: 1-866-840-1340

RANBAXY
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