PRODUCT MONOGRAPH

PrAPO-GLICLAZIDE

Gliclazide Tablets BP

80 mg

Hypoglycemic sulfonylurea

Oral hypoglycemic agent

APOTEX INC.
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Toronto, Ontario
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80 mg

Oral hypoglycemic agent

ACTIONS AND CLINICAL PHARMACOLOGY

Gliclazide is a hypoglycemic agent of the sulfonylurea group.

The hypoglycemic action of gliclazide 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.

Hemobiological properties of gliclazide have been observed in pharmacology studies. These are attributed to gliclazide action on the platelet behaviour, prostaglandin equilibrium and fibrinolysis.

Gliclazide is rapidly absorbed from the gastro-intestinal tract and the plasma peak of gliclazide occurs between 4 and 6 hours. In man it is highly bound to plasma proteins, about 94%. The mean elimination half-life in man approximates 10.4 hours.

Following oral administration the unchanged gliclazide in plasma is extensively metabolized with little of the unchanged compound (< 1%) appearing in the urine.

Gliclazide metabolites and conjugates are primarily eliminated via kidneys: 60 to 70%, and about 10 to 20% via faeces.

Some five principal metabolites have been identified in urine, essentially oxidized and hydroxylated derivatives, some as glucuronic acid conjugates.

Comparative Bioavailability

A standard, randomized, three-way crossover study was conducted in 21 healthy, adult, male volunteers under fasting conditions to evaluate the relative bioavailability of single oral doses (80 mg) of APO-GLICLAZIDE manufactured by Apotex Inc. and Diamicron® Tablets (80 mg) manufactured by Servier Canada Inc. The mean pharmacokinetic parameters of these subjects are listed:

Summary Table of the Comparative Bioavailability Data Gliclazide (Dose: 1 x 80 mg) (from measured data)			
Parameter	**Geometric Mean Arithmetic Mean (C.V.)**		**Ratio of Means (%) (CI)**
	APO-GLICLAZIDE	**Diamicron®†**	
$AUC_{0\text{-}60\ hr}$ (mcgAhr/mL)	53.197 56.554 (36.5)	54.489 57.653 (35.6)	97.6% (94.5 - 100.8%)
AUC_I (mcgAhr/mL)	55.813 60.190 (40.8)	57.570 61.853 (40.6)	97.0% (93.8 - 100.3%)
C_{max} (mcg/mL)	3.703 3.797 (22.3)	3.677 3.745 (19.8)	100.7% (95.6 - 106.0%)
T_{max} (hours)*	4.50 (30.6)	4.00 (28.5)	-

$T_{1/2}$ (hours)*	12.97 (27.3)	13.44 (30.7)	-

*Arithmetic means only (standard deviation)

†Diamicron® is manufactured by Servier Canada Inc. and was purchased in Canada.

Note: Although a three-way crossover bioavailability study was conducted, data will be provided for Apotex Lot No. XD292 and the Servier Canada Lot No. 8D0680 in support of this ANDS.

INDICATIONS

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.

CONTRAINDICATIONS

- Known hypersensitivity or allergy to APO-GLICLAZIDE (gliclazide), other sulfonylureas, sulfonamides, or to any of the excipients of this product (for a complete listing, see PHARMACEUTICAL INFORMATION, COMPOSITION section).
- Unstable and/or insulin dependent diabetes mellitus, particularly juvenile diabetes, diabetic ketoacidosis, diabetic pre-coma and coma.
- During stress conditions such as serious infection, trauma or surgery.
- In the presence of severe hepatic impairment.
- In the presence of severe renal impairment.
- Treatment with miconazole via systemic route or oromucosal gel (see DRUG INTERACTIONS).
- Pregnancy and lactation (see PRECAUTIONS, Pregnant Women and Nursing Mothers)

WARNINGS

The use of gliclazide will not prevent the development of complications peculiar to diabetes mellitus.

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

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. If a loss of adequate blood glucose-lowering response to gliclazide is detected, the drug should be discontinued.

PRECAUTIONS

Patients selection and follow-up

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.

In patients stabilized on gliclazide therapy, loss of blood sugar control may occur in cases of acute intercurrent disease, 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 and Drug-Herb Interactions). Under these conditions, discontinuation of gliclazide and administration of insulin should be considered.

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. Severe hypoglycemia can be induced by all sulfonylurea drugs. 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. Hypoglycemia is more likely to occur when caloric intake is inadequate or after strenuous or prolonged physical exercise. Some cases may be severe and prolonged. Hospitalisation may be necessary and glucose administration may need to be continued for several days. Hypoglycemia may be difficult to recognize in elderly patients and in patients receiving beta-blockers.

Possible other symptoms of hypoglycaemia are: intense hunger, lassitude, sleep disorders, agitation, aggression, poor concentration, reduced awareness and slowed reactions, depression, confusion, visual and speech disorders, aphasia, 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.

Usually, hypoglycaemic symptoms disappear after intake of carbohydrates (sugar). However, artificial sweeteners have no effect. Experience with other sulphonylureas shows that hypoglycaemia can recur even when measures prove effective initially. If a hypoglycaemic episode is severe or prolonged, and even if it is temporarily controlled by intake of sugar, immediate medical treatment or even hospitalisation are required.

Treatment with gliclazide can 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.

Other factors which increase the risk of hypoglycemia are: overdose of gliclazide, 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).

Dysglycaemia:

Fluoroquinolones should be used with caution in patients receiving gliclazide. Hypoglycaemia and hyperglycaemia have been reported in diabetic patients receiving concomitant treatment with fluoroquinolones, especially in elderly patients. Careful monitoring of blood glucose is recommended in all patients taking gliclazide and a fluoroquinolone concomitantly. (See DRUG INTERACTIONS).

Patients with Porphyria:
Cases of acute porphyria (which can cause severe abdominal pain, gastrointestinal symptoms, unspecified neurologic symptoms along with chronic, blistering lesions on sun-exposed skin) have been reported with the use of sulfonylurea drugs. Therefore, caution should be taken in the administration of gliclazide, as it may precipitate attacks of acute porphyria in patients with porphyria

Hematologic

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

Hepatic

The metabolism and excretion of sulfonylureas including gliclazide may 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, gliclazide is contraindicated in patients with severe hepatic impairment (See CONTRAINDICATIONS and PRECAUTIONS, Monitoring and Laboratory Tests).

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 treatment may be affected by fever, infection, surgical intervention or when used concomitantly with St. John's Wort (Hypericum perforatum) preparations. Closed monitoring is required in these patients.
In some cases, it may be necessary to administer insulin.

Hepatic function should be assessed before initiating therapy and the liver function should be assessed periodically in patients with mild to moderately impaired hepatic function. In patients with mild to moderately impaired renal function, renal function should be assessed periodically, blood and urine glucose should be regularly monitored. Measurements of glycated hemoglobin levels are recommended. Elderly patients (malnourished, with impaired hepatic, renal, or adrenal function) will require periodic monitoring and special care.

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 and administration of insulin should be considered.

Renal

The metabolism and excretion of sulfonylureas including gliclazide, may be slowed in patients with impaired renal function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted. Therefore, gliclazide is contraindicated in patients with severe renal impairment (See CONTRAINDICATIONS and PRECAUTIONS, Monitoring and Laboratory Tests).

Skin

Serious skin and hypersensitivity reactions including rash, pruritus, urticaria, angioedema, erythema, maculopapular rashes, bullous reactions (such as Stevens-Johnson syndrome, toxic epidermal necrolysis and bullous pemphigoid) and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported.

Bullous pemphigoid:

Cases of bullous pemphigoid requiring hospitalisation have been reported with the use of gliclazide (see ADVERSE REACTIONS). In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the gliclazide. Tell patients to report development of blisters or erosions while receiving gliclazide. If bullous pemphigoid is suspected, gliclazide should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

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 mothers:

The product is contra-indicated 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 contra-indicated in breast-feeding mothers (see CONTRAINDICATIONS).

Pediatric use**:**

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

Geriatrics:

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

DRUG INTERACTIONS

As a result of drug interaction, hypoglycemia may be potentiated when a sulfonylurea is used concurrently with agents such as: long-acting sulfonamides, tuberculostatics, clarithromycin, phenylbutazone, clofibrate, monoamine oxidase inhibitors, coumarin derivatives, salicylates, non-steroidal anti-inflammatory agents, probenecid, beta-blockers, miconazole (see CONTRAINDICATIONS), azole antifungal agents (oral and parenteral preparations), H2-receptor antagonists, disopyramide and angiotensin converting enzyme inhibitors. In addition, while not approved for use with other antidiabetic agents,

hypoglycemia is potentiated when gliclazide is used in combination with other antidiabetic agents.

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

Concomitant use of fluoroquinolones and gliclazide may cause hypoglycaemia and hyperglycaemia. Elderly patients may be more sensitive to this interaction. In case of concomitant use of gliclazide and a fluoroquinolone, the patient should be warned of this risk and the importance of blood glucose monitoring should be emphasized.

Combination with anticoagulant therapy (warfarin and other) must be taken into account because sulfonylureas may lead to potentiation of anticoagulation during concomitant treatment. Adjustment of the anticoagulant dosage may be necessary.

Intolerance to alcohol (disulfiram-like reaction: flushing, sensation of warmth, giddiness, nausea and occasionally tachycardia) may occur in patients treated with a sulfonylurea. This reaction can be prevented by avoiding the use of alcohol. Alcohol increases the hypoglycaemic reaction (by inhibiting compensatory reactions) that can lead to the onset of hypoglycaemic coma. Avoid alcohol or medicines containing alcohol.

<u>Drug-Herb Interactions</u>

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

ADVERSE REACTIONS

In clinical trials involving about 2000 patients treated with gliclazide, the overall incidence of adverse reaction was 10.5%; this necessitated the discontinuation of therapy in 1.2% of patients.

Adverse Drug Reaction Overview

The most frequently reported adverse drug reactions during long-term studies and postmarket experience are hypoglycaemia (see WARNINGS AND PRECAUTIONS) and gastrointestinal disturbances (including abdominal pain, nausea, vomiting, dyspepsia, diarrhea, constipation).

Hypoglycemia (see PRECAUTIONS):

Weakness, nervousness, shakiness and paresthesia have been reported. 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.

Gastro-intestinal reactions:

Nausea, vomiting, diarrhea, epigastric fullness and gastric irritation can be observed. These reactions are generally dose-related and may disappear when the dose is reduced.

Hepatobiliary reactions:

With sulfonylureas cases were also observed of elevated liver enzyme levels (AST, ALT, alkaline phosphatise) and even impairment of liver function with cholestasis and jaundice and hepatitis which regressed after withdrawal of the sulfonylurea or led to life-threatening

liver failure in isolated cases. Rare cases of jaundice have been reported. Discontinue treatment if cholestatic jaundice appears.

Dermatological reactions:

Allergic reactions such as pruritus, erythema, urticaria and morbiliform or maculopapular rash have been reported. These reactions may persist during treatment, which must then be interrupted. Cases of cutanea porphyria tarda and of photosensitivity have also been described with sulfonylurea drugs.

Hematological reactions:

As with all hypoglycemic sulfonylurea drugs, a few rare cases have been reported of leukopenia, erythrocytopenia agranulocytosis, thrombocytopenia, haemolytic anemia, pancytopenia and allergic vasculitis.

Metabolic reactions:

Cases of hepatic porphyria and disulfiram-like reactions have been described with sulfonylurea drugs. Clinical experience to date has shown that gliclazide has a low incidence of disulfiram type reactions.

Cardiovascular:

Arteritis, cardiac failure, cerebrovascular disorder, coronary artery disorder, epistaxis, hypotension, myocardial infarction, oedema legs, palpitation, tachycardia, thrombophlebitis, vein disorder.

Endocrine reactions:

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 during a study involving 15 patients.

Laboratory tests:

The pattern of laboratory tests abnormalities observed with gliclazide was similar to that for other sulfonylureas. Occasional mild to moderate elevations of SGOT, 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.

Post-Market Adverse Drug Reactions:

In post-marketing experience with gliclazide, the most frequently reported adverse drug reaction is hypoglycaemia.

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

Gastrointestinal disturbances, 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, toxic epidermal necrolysis and bullous pemphigoid) and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported.

The following adverse events have also been observed with gliclazide: cases of erythrocytopenia, agranulocytosis, haemolytic anemia, allergic vasculitis, hyponatremia, and elevated liver enzyme levels (AST, ALT, alkaline phosphatise); 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.

SYMPTOMS AND TREATMENT OF 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:

Discontinue medication and treat hypoglycemia by giving dextrose promptly and in sufficient quantity.

Some sulfonylurea-induced hypoglycemias may be refractory to treatment and susceptible to relapse especially in elderly or malnourished patients. Continuous dextrose infusions for hours or days have been necessary.

Strict monitoring should be continued until the doctor is sure that the patient is out of danger.

Severe hypoglycaemic reactions, with coma, convulsions or other neurological disorders are possible and must be treated as a medical emergency, requiring immediate hospitalisation. If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid I.V. injection of 50 mL of concentrated glucose solution (20 to 30 %). This should be followed by continuous infusion of a more dilute glucose solution (10 %) at a rate that will maintain blood glucose levels above 1 g/L. Patients should be monitored closely and, depending on

the patient's condition after this time, the doctor will decide if further monitoring is necessary.
Dialysis is of no benefit to patients due to the strong binding of gliclazide to proteins.

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

DOSAGE AND ADMINISTRATION

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

The recommended daily dosage of APO-GLICLAZIDE (gliclazide) is 80 to 320 mg (1 to 4 tablets). Dosage of 160 mg and above should be divided into two equal parts for twice a day administration. APO-GLICLAZIDE should be taken preferentially with meals.

The recommended starting dose of APO-GLICLAZIDE is 2 tablets per day (160 mg) taken as one tablet twice a day with meals. The total daily dose should not exceed 320 milligrams.

Patients with renal or hepatic impairment may require dosage reduction (See PRECAUTIONS, Hypoglycemic reactions).

In patients where on initial trial the maximal recommended dose fails to lower blood glucose adequately, the drug should be discontinued. During the course of therapy a loss of effectiveness may occur.

It is advisable to ascertain the contribution of the drug in control of the blood glucose by discontinuing the medication semi-annually or at least annually with careful monitoring of the patient. If the need for the drug is not evident, the drug should not be resumed. In some

diabetic subjects, short-term administration periods of the drug may be sufficient during periods of transient loss of blood sugar controls.

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 APO-GLICLAZIDE therapy after cessation of insulin. If a change from insulin to APO-GLICLAZIDE 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.

HOW SUPPLIED

APO-GLICLAZIDE (gliclazide) Tablets, 80 mg: Round, white, flat-faced bevelled-edge tablets, engraved “80” on one side, cross-scored on the other side. Available in bottles of 100 and 500 tablets, unit-dose packages of 60 and 100 tablets.

INFORMATION TO THE PATIENT

Full prescribing information is available to the physicians and pharmacists.

APO-GLICLAZIDE is available only with your physician's prescription.

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

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

Before you begin treatment with this medicine, you and your doctor should talk about the good medicine will do as well as the risks of using it. You should also find out about other possible ways to control your diabetes such as diet alone or by diet plus insulin.

Use only as specifically directed. Do not alter the dosage unless ordered to do so by your physician.

Before using this medicine

APO-GLICLAZIDE may cause low blood sugar (hypoglycemia). You should ask your doctor, pharmacist or diabetes educator about symptoms of low blood sugar and what to do if you experience these symptoms. You should also test your blood sugar as instructed by your doctor.
Before you use APO-GLICLAZIDE talk to your doctor or pharmacist 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 porphyria (genetic disease in which your body builds-up chemicals with skin, nervous system or other symptoms)

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

Driving and Operating Machinery:

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

Proper use of this medicine

Follow carefully the special meal plan your physician gave you. This is the most important part of controlling your condition and is necessary if the medicine is to work properly.

Take APO-GLICLAZIDE with a meal as directed by your physician. Do not take more nor less of it than your doctor ordered, and take it at the same time each day. If you miss a dose of this medicine, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double doses.

APO-GLICLAZIDE is contraindicated (must not be taken) in the following conditions:

- Allergy or hypersensitivity to gliclazide, other sulphonylureas, sulphonamides or to any of the excipients of this product.
- Unstable and/or insulin-dependent diabetes mellitus (type I diabetes), particularly juvenile diabetes, diabetes ketoacidosis, diabetes pre-coma and coma.
- Stressful conditions such as serious infection, trauma or surgery.
- Severe liver impairment.
- Severe kidney impairment.
- Treatment with miconazole.
- Pregnancy and/or breast-feeding.

The safety of APO-GLICLAZIDE in adolescents and children has not been established.

APO-GLICLAZIDE is prescribed for your specific medical problem and for your own use only. Do not give to other people.

Keep all medicines out of the reach of children.

Precautions while using this medicine

Your physician should check your progress at regular visits, especially during the first few weeks that you take this medicine. Please keep your appointments.

Test for sugar in your blood or urine as directed by your physician. This is a convenient way to make sure your diabetes is being controlled and provides an early warning when it is not.

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

Drugs that may interact with APO-GLICLAZIDE are:
Other antidiabetic agents, long-acting sulfonamides, tuberculostatics, clarithromycin, NSAIDs, fibrates, monoamine oxidase inhibitors, salicylates, probenecid, beta-blockers, azole antifungal agents (oral and parenteral preparations), H2-receptor antagonists and angiotensin converting enzyme inhibitors, anticoagulants, barbiturates and fluoroquinolones. Certain drugs tend to induce hyperglycemia and may lead to loss of blood sugar control. These include diuretics (thiazides, furosemide), corticosteroids, oral contraceptives (estrogen plus progestogen), chlorpromazine, ritodrine, salbutamol, terbutaline, danazol and nicotinic acid in pharmacologic doses. Low blood sugar and high blood sugar can occur when a medicine belonging to a class of antibiotics called fluoroquinolones is taken at the same time as APO-GLICLAZIDE, 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.

Herbs that may interact with APO-GLICLAZIDE are:

- Saint John's Wort preparations tend to cause high blood sugar and may lead to loss of blood sugar control.

Serious Skin Reactions (DRESS, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, bullous pemphigoid, 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 have been reported in patients taking APO-GLICLAZIDE. 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.

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

Inform your physician about any illness which may develop during your treatment with APO-GLICLAZIDE and about any new prescribed or non-prescribed medication you may be taking.

Side effects of this medicine

Along with their needed effects, oral antidiabetes medicines may cause some unwanted effects.

The more frequently reported side effects during clinical trials with APO-GLICLAZIDE were hypoglycemia (low blood sugar) and indigestion or stomach upsets.

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

In addition, some uncommon serious side effects/symptoms may happen and you should stop taking the drug and talk with your doctor or pharmacist in all cases: unexplained fever chills or sore throat; yellowing of skin or eyes, dark-coloured urine or light-coloured bowel movements (e.g. jaundice) which in most cases disappeared after withdrawal of the drug, but may lead to life-threatening liver failure in isolated cases; 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 cases of the following have been reported: 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); widespread blistering or peeling of the skin.

Serious Skin Reactions (DRESS, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, bullous pemphigoid, 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 have been reported in patients taking APO-GLICLAZIDE. 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 seek urgent advice from a doctor or pharmacist and tell him that you are taking this medicine.

Additional information on APO-GLICLAZIDE may be obtained from your physician or pharmacist.

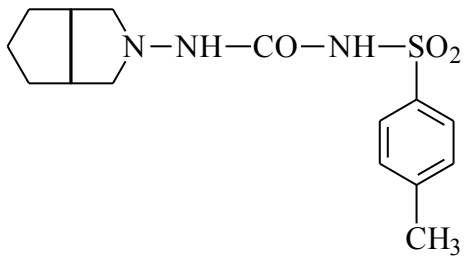
PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: Gliclazide

Chemical Name: 1-(3-Azabicyclo[3.3.0]-oct-3-yl)-3-(p-tolylsulfonyl)urea

Structural Formula:



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

Molecular Weight: 323.42 g/mol

Solubility: Practically insoluble in water; freely soluble in dichloromethane; sparingly soluble in acetone.

pKa: 5.8

Partition Coefficient:

pH	% gliclazide in organic phase (water/CHCl 3)
0 to 7	almost 100%
8.6	80%
9.0	55%
10.0	12%

Melting Point: Approximately 168°C.

Description: White, crystalline, virtually odourless powder.

Composition:

Each tablet of APO-GLICLAZIDE (gliclazide) contains the following non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

Stability and Storage Recommendations: APO-GLICLAZIDE (gliclazide) should be stored at room temperature 15°C to 30°C. Preserve in well closed containers.

PHARMACOLOGY

see Published Review by HOLMES et al. (Drugs 1984)

HUMAN PHARMACOLOGY

1. Pharmacokinetics and metabolism

Absorption: Gliclazide is extensively absorbed from the gastrointestinal tract. Following oral administration of 3 mg/kg of gliclazide to four healthy subjects, the peak plasma levels (mean 5.0 mcg/mL) were achieved between 4 to 6 hours. The absorption half-life in man is 1.3 hours.

Distribution: The mean apparent volume of distribution in 4 healthy subjects was 20 to 40% of bodyweight.

Protein binding: Using equilibrium dialysis, it was shown that the majority of the drug is protein bound. At a plasma concentration of about 8 mcg/mL, 94.2% of the drug was protein bound and 5.8% was free.

Metabolism: Although more than 90% of unchanged gliclazide is found in plasma following administration, this is intensively metabolized with little of the unchanged compound (< 1%) found in urine. Five principal metabolites have been found in urine, essentially oxidized and hydroxylated derivatives, the majority of which undergo glucuroconjugation.

Excretion: Gliclazide is essentially eliminated via the urine: 60 to 70% as against 10 to 20% via faeces.

Half life: The mean elimination half-life is 10.4 h.

2. Pharmacodynamics

Gliclazide acts primarily by enhancing the release of endogenous insulin. Residual function of beta-cells is therefore necessary for its action. Clinical studies demonstrate that the sulphonylureas are ineffective in completely pancreatectomized patients and in juvenile onset diabetic subjects. The mechanism of action is not fully understood. Sulphonylureas including gliclazide cause degranulation of the pancreatic beta-cells; a phenomenon associated with increased rate of insulin secretion.

Extrapancreatic effects of sulphonylureas have been reported and certain of these may potentiate the effects of secreted insulin. These effects include reduction in hepatic uptake of endogenous insulin and increased sensitivity of peripheral tissues to insulin. Sulphonyl-urea agents may stimulate hyperplasia of the beta-cells.

At normal therapeutic doses gliclazide has been shown in man to reduce platelet adhesiveness and aggregation. When these are close to normal at the inclusion time, no significant difference is observed.

ANIMAL PHARMACOLOGY

1. Pharmacokinetics and metabolism

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

Blood Kinetics of Gliclazide (PO) in Different Species (single doses)

Species	Number of Subjects / Doses	Absorption $T_{1/2}$ (h)	Plasma Peak (h)	Volume of Distribution (% body weight)	Plasma Half-Time (h)
Man	4 3 mg/kg	1.3 (1)	4-6 (1)	36.3 (1) -	10.4 (1) -
Monkey	4 3 & 50 mg/kg	0.3 (1)	1-2 (1)	24.4 (1) 108 (4)	2.9 (1) 6.2 (4)
Beagle	3 3 & 50 mg/kg	0.7 (1)	2-6 (1)	21.3 (1) 22 (4)	10.7 (1) 9.9 (4)
Rabbit	5 10 & 25 mg/kg	0.7 (2)	3 (2)	30.8 (2) 51.8 (3)	3.9 (2) 5.9 (3)
Rat	5 10 mg/kg	0.5 (2)	1 (2)	53.8 (2) -	2.5 (2) -

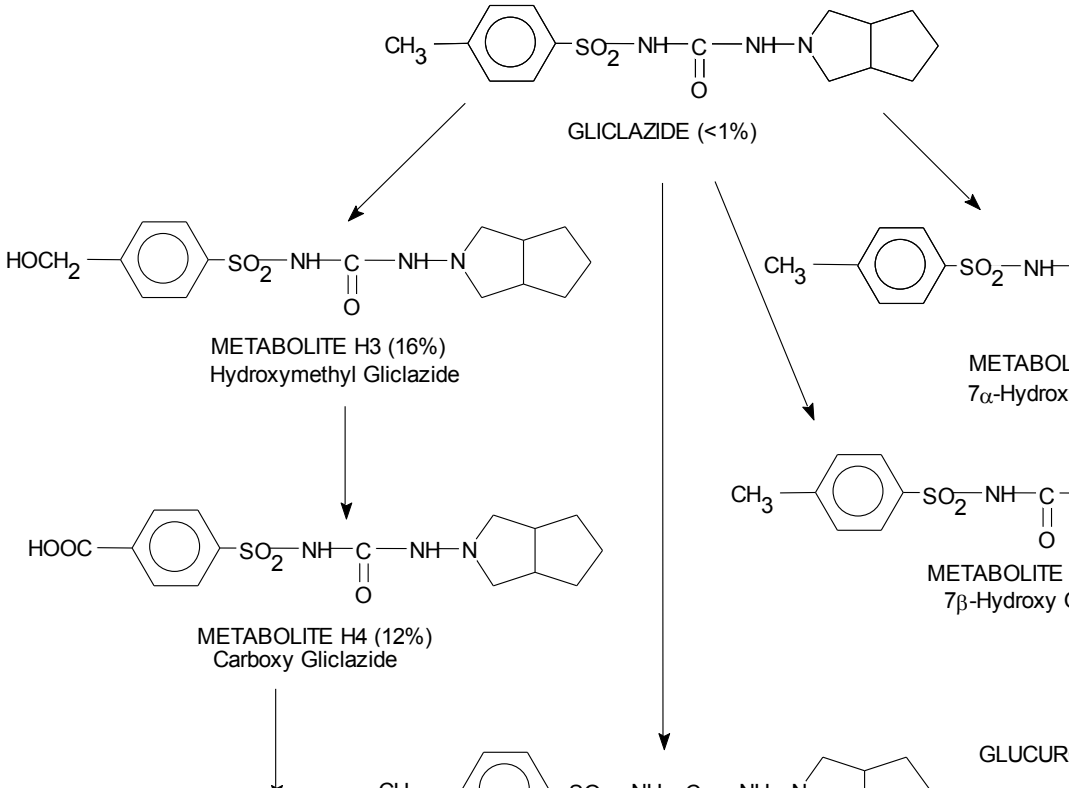
(1) = 3 mg/kg PO, (2) = 10 mg/kg PO, (3) = 25 mg/kg PO, (4) = 50 mg/kg PO

Gliclazide is rapidly absorbed in all species, with a plasma peak observed between 1 and 6 hours. More than 90% of gliclazide is found unchanged in the plasma. Elimination from plasma is monophasic with inter-species variations concerning half-life (2.5 hours in the rat, 10.4 hours in man).

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

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

The principal metabolic pathways of gliclazide may be summarized as follows:



2. 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.

3. Haemovascular 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

1) The platelet behaviour: reduction of the platelet adhesiveness in the diabetic rabbit of platelet aggregation induced by ADP or by collagen in the rabbit.

2) The prostaglandin equilibrium: inhibition of the acid arachidonic release and *in vitro* thomboxan synthesis and increase of the PGI_2 production.

3) The parietal fibrinolysis: increase of the release of the parietal plasminogen activator (t.PA). This activator, of an endothelial origin, acts on the plasmin which is the enzyme degrading the fibrin.

4. Other actions

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

TOXICOLOGY

see Published Review by HOLMES et al (DRUGS 1984)

1. Acute toxicity

Species	Mean Weight	Number of animals per lot	LD_{50} mg/kg	
Mouse CD-SPF	25 g	10 M 10 F	> 3000	
Mouse ICR-HAN	20 g	10 M 10 F	> 4000	
Rat SD-SPF	250 g	10 M	3733 〈 5200 2679	
		10 F	3407 〈 5467 2123	
Rat CFY	110 g	6 M 6 F	> 4000	
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. 750 times the therapeutic dose) and than 2000 mg/kg in the guinea-pig (i.e. 500 times the therapeutic dose). Symptomatology is essentially linked to the hypoglycemic effect of the drug.

2. Sub-chronic toxicity

- Maximum tolerated dose:

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

- Four-week oral toxicity study in the Beagle dog**:**

  Groups of 4 Beagle dogs (2 males, 2 females), were treated for 30 days with 0, 15, 30, 45 or 90 mg/kg/day.

  At the dose of 90 mg/kg, 2 animals died as a result of prolonged hypoglycemic coma following 2 weeks of treatment.

  All others showed normal behaviour, with the exception of an increase in the weight of the liver. No evidence was found of any change in biochemical (apart from the fall in blood glucose), haematological 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, haematological and histopathological results.

3. 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 behaviour and haematological results. From a biochemical standpoint, blood urea decreased significantly in the male rats as did blood glucose in the males of the 100 mg/kg/day group.

  Histological examination showed an increase in the weight of the liver and kidneys in male animals, not accompanied by any histological lesion.

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

- Six-month study in the Beagle dog:

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

From a clinical standpoint:

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

From a laboratory standpoint:

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

From a histological standpoint:

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

- Twelve-month oral toxicity study in the Beagle dog:

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

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

- Twelve-month oral toxicity study in the rhesus monkey:

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

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

TERATOGENICITY

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

- In the CD/SPF mouse (group of 30 females), administration of gliclazide at doses of 0, 50, 200 and 500 mg/kg/day starting from mating and throughout gestation did not modify fertilization and abortion rates and had no apparent teratogenic effect.

- In the CFY-SPF rat (groups of 20 females), administration of gliclazide at doses of 0, 50, 100 and 200 mg/kg/day from the 6th to the 15th day of gestation did not show any embryotoxic effect.

- In the SD/SPF rat (groups of 60 females), administration of gliclazide at the doses of 0, 15, 60, 120, 240 and 480 mg/kg/day 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 renal lesions accompanied by anorexia and weight loss. However, there was no evidence of any teratogenic effect.

FERTILITY AND REPRODUCTION

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

There was no evidence of any change in fertilization or 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

The mutagenic potential of gliclazide has been sought using five 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).

GENE MUTATION TESTS

1st Ames 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 Ames 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 TEST

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.

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 is marketed for numerous years all over the world and in particular in Europe and Japan without any suspicion of carcinogenicity.

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