PRODUCT MONOGRAPH

AVA-GLICLAZIDE

Gliclazide Tablets BP

80 mg

Oral Hypoglycemic Agent

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THERAPEUTIC CLASSIFICATION

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 and 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 gastrointestinal 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 feces.

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 AVA-GLICLAZIDE 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)
	AVA-GLICLAZIDE	Diamicron®†	
$AUC_{0\text{-}60\ hr}$ (mcg≙hr/mL)	53.197 56.554 (36.5)	54.489 57.653 (35.6)	97.6% (94.5 - 100.8%)
AUC_I (mcg·hr/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.

INDICATIONS AND CLINICAL USE

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 AVA-GLICLAZIDE (gliclazide). Unstable and/or insulin dependent diabetes mellitus, ketoacidosis, coma. During stress conditions such as serious infection, trauma or surgery. In the presence of liver disease or renal impairment. Pregnancy.

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.

Patients over a period of time, may become progressively less responsive to therapy with oral hypoglycemic agents because of worsening of their diabetic state. If a loss of adequate blood glucose-lowering response to gliclazide is detected, the drug should be discontinued.

PRECAUTIONS

Patient 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 or in stressful situations such as trauma or surgery. Under these conditions, discontinuation of gliclazide and administration of insulin should be considered.

The metabolism and excretion of sulfonylureas including gliclazide, may be slowed in patients with impaired renal and/or hepatic function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted. In such patients, blood and urine glucose should be regularly monitored.

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.

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, phenylbutazone, clofibrate, monoamine oxidase inhibitors, coumarin derivatives, salicylates, probenecid, propranolol, miconazole, cimetidine, disopyramide and angiotensin converting enzyme inhibitors.

Certain drugs tend to induce hyperglycemia and may lead to loss of control of blood sugar control. These include diuretics (thiazides, furosemide), corticosteroids, 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.

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.

Nursing 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, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

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.

Hypoglycemia (See Precautions)

As with other sulfonylurea drugs, manifestations of hypoglycemia including dizziness, lack of energy, drowsiness, headache and sweating have been observed. Weakness, nervousness, shakiness and paresthesia have also been reported. Severe hypoglycemia which mimics acute CNS disorders may occur. Hepatic and/or renal disease, malnutrition, debility, advanced age, alcoholism, adrenal or pituitary insufficiency may be predisposing factors.

Gastrointestinal 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

Rare cases of jaundice have been reported.

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, agranulocytosis, thrombocytopenia and anemia.

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.

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.

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.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with AVA-GLICLAZIDE (gliclazide) or any other hypoglycemic agent. Determination of the proper dosage for AVA-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 AVA-GLICLAZIDE (gliclazide) is 80 to 320 mg (1 to 4 tablets). Dosages of 160 mg and above should be divided into two equal parts for twice a day administration. AVA-GLICLAZIDE should be taken preferentially with meals.

The recommended starting dose of AVA-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.

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 AVA-GLICLAZIDE therapy. If a change from insulin to AVA-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.

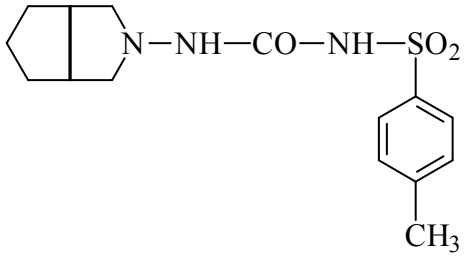
PHARMACEUTICAL INFORMATION

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

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

STABILITY AND STORAGE RECOMMENDATIONS

AVA-GLICLAZIDE (gliclazide) should be stored at room temperature (15 - 30°C). Preserve in well closed containers.

AVAILABILITY OF DOSAGE FORM

AVA-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 tablets.

INFORMATION FOR THE PATIENT

Full prescribing information is available to the physicians and pharmacists.

AVA-GLICLAZIDE is available only with your physician's prescription. It belongs to the family of hypoglycemic (antidiabetic) medicines which are taken by mouth to help reduce the amount of sugar in the blood. It is to be used as an adjunct to a medically recom-mended and carefully supervised diet and regimen of exercise compatible with your state of health.

Before you begin treatment with this medicine, you and your doctor should talk about the good the 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 by 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.

Your physician may want you to carry an identification card or wear a bracelet or necklace stating that you are using this medicine.

Before Using This Medicine

To decide on the best treatment for your medical problem, your physician should be told if:

- you have already taken AVA-GLICLAZIDE or any other anti-diabetic medicine and if you have developed an allergy or any intolerance to it or to sulfonamide (sulfa) medications, including thiazide diuretics.
- you suffer from any other conditions, in particular kidney or liver diseases.
- you are pregnant or intend to become pregnant or are breast feeding or intend to breast feed.

- you are taking any other medication with or without a prescription.

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 AVA-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.

AVA-GLICLAZIDE is contraindicated (must not be taken) during pregnancy.

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

AVA-GLICLAZIDE is prescribed for your specific medical problem and for your own use only. Do not give it 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 AVA-GLICLAZIDE.

Avoid drinking alcoholic beverages until you have discussed their use with your doctor. Some patients who use alcohol while taking this medicine may suffer stomach pains, nausea, vomiting, dizziness, pounding headache, sweating, or flushing (redness of face and skin). In addition, alcohol may produce a drop in blood sugar (hypoglycemia).

Inform your physician about any illness which may develop during your treatment with AVA-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 AVA-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 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).

Rarely, allergic reactions may occur; if you suspect these consult your doctor.

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

PHARMACOLOGY

HUMAN PHARMACOLOGY

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 μg/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 μg/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 feces.

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

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

Pharmacokinetics and Metabolism

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

Blood Kinetics of Gliclazide (PO) in Different Species (single doses)					
Species	**Number of Subjects (Doses)**	**Absorption $T_{½}$ (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) -

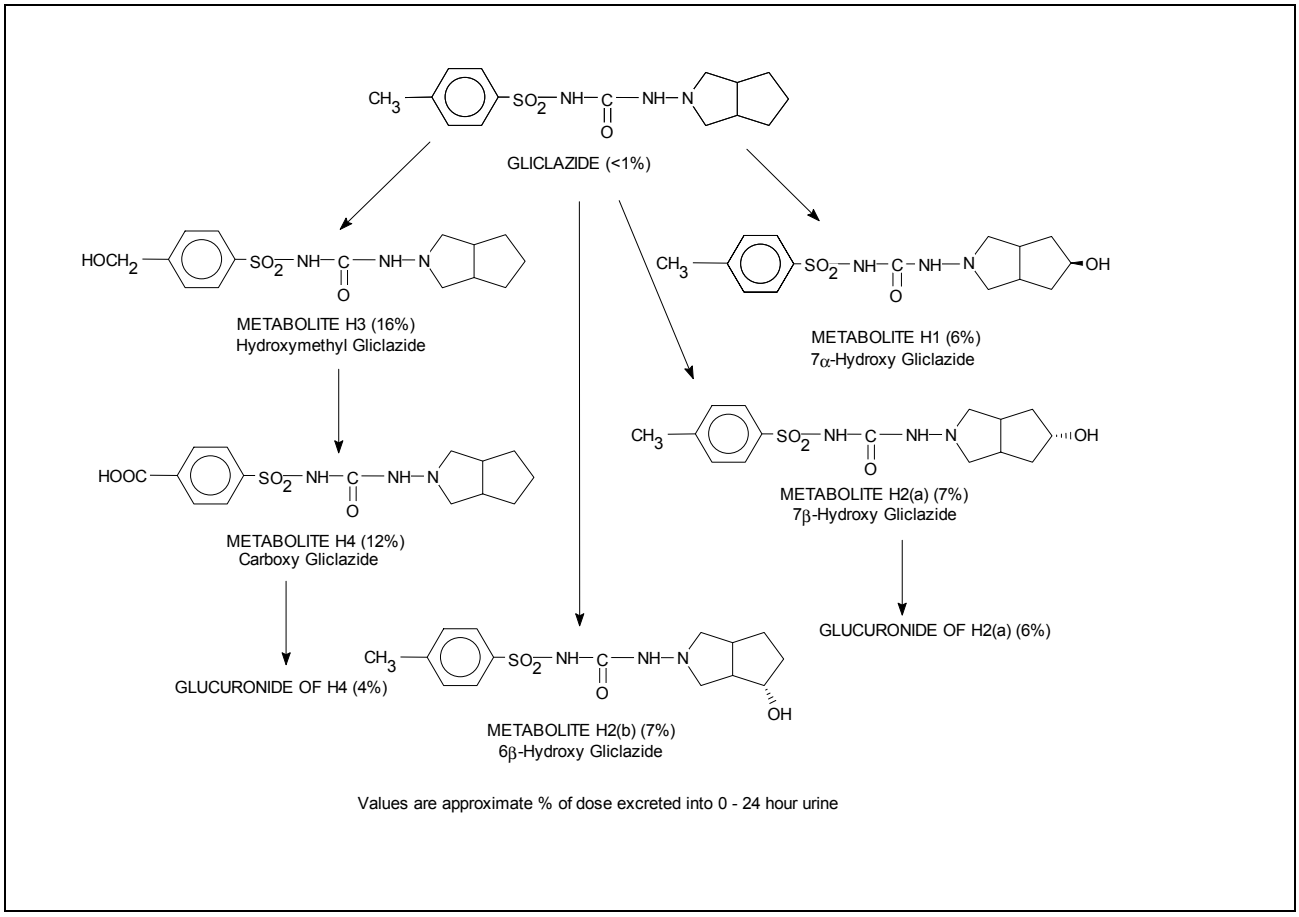
(1) = 3 mg/Kg PO, (2) = 10 mg/Kg PO, (3) = 25 mg/Kg PO, (4) = 50 mg/Kg PO

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 feces.

The drug is extensively 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:



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 potentializes 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:

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.

Other Actions

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

TOXICOLOGY

Acute Toxicity

Species	Mean Weight	Number of Animals Per Lot	LD_{50} mg/Kg	
Mouse CD-SPF	25 g	10 M 10 F	> 3000	
Mouse ICR-HAN	20 g	10 M 10 F	> 4000	
Rat SD-SPF	250 g	10 M	3733 ⟨ 5200 2679	
		10 F	3407 ⟨ 5467 2123	
Rat CPY	110 g	6 M 6 F	> 4000	
Tricolour 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.

Sub-chronic Toxicity

Maximum Tolerated Dose

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

Four-Week Oral Toxicity Study in the Beagle Dog

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

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

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

Two-Month Oral Toxicity Study in the Guinea-Pig

Groups of 10 guinea-pigs (5 males, 5 females), were treated 6 days out of 7 for 2 months with 0, 25, 50 or 100 mg/Kg/day.

Only male animals in the 50 mg/Kg group showed delayed weight gain.

All others had normal biochemical, hematological and histopathological results.

Chronic Toxicity

Six-Month Study in the Sprague-Dawley Rat

Groups of 20 rats (10 males, 10 females) weighing 300 g, were treated for 6 days out of 7 for 6 months with 0, 25, 100 or 200 mg/Kg/day.

Seven deaths occurred as a result of technical problems.

All other animals showed normal behaviour and hematological 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 erythrocyte counts, hematocrit values and hemoglobin concentrations at doses of 200 mg/Kg and higher.

Six-Month Study in the Beagle Dog

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

From a Clinical Standpoint:

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

From a Laboratory Standpoint:

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

From a Histological Standpoint:

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

Twelve-Month Oral Toxicity Study in the Beagle Dog

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

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

Twelve-Month Oral Toxicity Study in the Rhesus Monkey

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

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

TERATOGENICITY

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

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

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

In the SD/SPF rat (groups of 60 females), administration of gliclazide at the doses of 0, 15, 30, 60, 120, 240 and 480 mg/Kg/day throughout gestation had no effect on fertilization, gestation, mean number of fetuses or incidence of fetal abnormalities. The number of offspring surviving at 48 hours was decreased in the 15, 60, 120 and 480 mg/Kg groups. No other abnormality was seen.

In the common rabbit (group of 15 females), administration of gliclazide at doses of 0, 10, 25 and 50 mg/Kg/day from the 6th to the 18th day of gestation had no effect on the number of fetal resorptions, percentage of abortion nor the mean number of fetuses per litter.

In the New Zealand rabbit (group of 6 females), administration of gliclazide at doses of 0, 50, 75, 100 and 200 mg/Kg/day for 13 days followed by an observation period of 8 days, was associated with maternotoxicity and embryotoxicity in the form of gastro-intestinal and renal lesions accompanied by anorexia and weight loss. However, there was no evidence of any teratogenic effect.

FERTILITY AND REPRODUCTION

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

There was no evidence of any change in fertilization nor abortion rates. Fetal resorption, placental hemorrhage and fetal atrophy rates were unaffected. The genital tract of treated parents showed no abnormality imputable to treatment.

No embryotoxic effect was seen on fetuses of females sacrificed before littering.

In females in which gestation was allowed to run to term, a significant decrease in the viability of offspring was seen at 48 hours.

No abnormality was seen during the study of fertility and reproduction in first generation offspring born of treated animals.

MUTAGENICITY

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

REFERENCES

1) Campbell DB, Adriaenssens PI, Hopkins YW, Gordon B, Williams JRB. Pharmacokinetics and metabolism of Gliclazide. A review. Royal Soc Med Int Congr Symp 1980; 20: 71-82.

2) Campbell B, Gordon BH, Ings RMJ, Beaufils M, Meyrier A, Jones R. The effect of renal disease on the pharmacokinetics of gliclazide in diabetic patients. Br J Clin Pharmacol 1986; 21(5): 572-573.

3) Chan TK, Chan V, Teng CS, Yeung RTT. 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.

4) Desnoyers P, Saint-Dizier D. The pharmacology of S 1702, a new highly effective oral antidiabetic drug with unusual properties. Arzneimittelforsch 1972; 22: 1691-1695.

5) Duhault J, Lebon F. Protective activity of S 1702 on the microvascular system in normal and diabetic rats. Arzneimittelforsch 1972; 22: 1686-1690.

6) Fujitani B, Maeda J, Tsuboi T, et al. Effect of gliclazide on prostaglandin I_2 formation in normal streptozotocin-induced diabetic animals. Jpn J Pharmacol 1983; 33; 965-970.

7) Golay A, Broquet C, Chabot V, Studer S, Felber J P. Effets métaboliques du gliclazide chez le diabétique de type II. Etude par calorimétrie indirecte. Schweiz Med Wochenschr 1984; 114(8):261-264.

8) 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.

8) Holmes B et al. Gliclazide. A preliminary review of its pharmacodynamic properties and therapeutic efficacy in diabetes mellitus. Drugs 1984; 27: 301-327.

10) Jerums G et al. Lack of effect of gliclazide on early diabetic nephropathy and retinopathy: a two-year controlled study. Diabetes Res Clin Pract 1987; 3: 71-80.

11) Larkins R, Jerums G, Taft JL, Godfrey H, Smith IL, Martin TJ. Lack of effect of gliclazide on platelet aggregation in insulin-treated and non-insulin treated diabetes: a two-year controlled study. Diabetes Res Clin Pract 1988; 4: 81-87.

12) Malaisse WJ, Couturier E, Valverde I. The insulinotropic action of gliclazide: possible mode of action. Royal Soc Med Int Congr Symp 1980; 20: 37-42.

13) 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.

14) Quatraro A, Consoli G, Ceriello A, Giugliano D. 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.

15) Regnault F. Gliclazide in the treatment of diabetic retinopathy. Adv Exp Med Biol 1979; 119: 443-448.

16) Serradas P, Bailbe D, Portha B. Long-term gliclazide treatment improves the *in vitro* glucose-induced insulin release in rats with type 2 (non-insulin-dependent) diabetes induced by neonatal streptozotocin. Diabetologia Sept. 1989 in-press.

17) Product Monograph. Diamicron® (gliclazide) 80 mg Tablets - Oral Hypoglycemic Agent. Servier Canada Inc., March 15, 1990.