PRODUCT MONOGRAPH

Rhoxal-gliclazide

(gliclazide tablets, BP)

80 mg Tablets

Oral hypoglycemic agent

Rhoxalpharma Inc.
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Date of Preparation:
June 3, 2004

Control No.: 091965

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ACTION AND CLINICAL PHARMACOLOGY

Rhoxal-gliclazide (gliclazide) is a second generation oral hypoglycemic agent of the sulphonylurea 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.

In pancreatectomized dogs, the drug showed no activity either following oral or intravenous injections, suggesting that the drug has a direct action on the pancreas to increase insulin secretion.

In animals and in humans, gliclazide has been shown to also cause

reduction of platelet adhesiveness and aggregation, altered prostaglandin metabolism, as well as increased fibrinolytic activity.

Gliclazide is rapidly absorbed from the gastro-intestinal tract and the plasma peak of gliclazide occurs within 4 hours.

In man, at therapeutic levels, the drug is highly bound (93%) to plasma proteins when compared to dogs (87%) and rabbits (89%). The relatively low volume of distribution (36% of body weight) suggests only limited tissue distribution, which could be in part explained by the extent of protein binding.

The mean elimination half-life in man approximates 10.4 hours; however, there was considerable variation in elimination half-lives ranging from 6.1 hours to 14.3 hours.

Following oral administration, the unchanged gliclazide in plasma is extensively metabolized with less than 20% of the dose being excreted as unchanged drug. As with other sulphonylureas, gliclazide is oxidized to produce either hydroxylated metabolites or N-oxygenated compounds and the corresponding alcohol and carboxylic acid.

Gliclazide metabolites and conjugates are primarily eliminated via kidneys (60 to 70%) and feces (10 to 20%). Five principal metabolites have been identified in the urine.

A comparative, bioavailability study was conducted to compare the rate and extent of absorption of Rhoxal-gliclazide 80 mg tablets against the Canadian Reference gliclazide 80 mg tablets. The pharmacokinetic data calculated for Rhoxal-gliclazide and Canadian Reference Product are presented below:

MEAN PHARMACOKINETIC DATA

Parameter	Geometric Mean Arithmetic Mean (C.V)		Ratio of Means (%)[A]
	Rhoxalpharma (A)	Diamicron® (B)	
AUC (0-t hrs.) (ng.hr/mL)	45593.94 49356.82 (40.18)	43682.30 46356.29 (39.77)	104.38
AUC (0-infinity) (ng.hr/mL)	52445.70 58551.52 (50.09)	50297.43 55376.52 (49.17)	104.27
C_{max} (ng/mL)	2607.34 2703.58 (25.96)	3065.36 3226.45 (32.55)	85.06
T_{max} (hours)*	8.75 (2.60)	8.17 (2.76)	--
$t_{1/2}$ (hours)*	14.86 (4.86)	14.89 (6.31)	--
K_{el} ($hour^{-1}$)*	0.050 (0.013)	0.053 (0.019)	--

*These are arithmetic means (standard deviation).
[A]Calculated using geometric means according to the formula: $e^{(\text{Rhoxalpharma (A)-Diamicron® (B)})} \times 100\%$

INDICATIONS AND CLINICAL USE

Rhoxal-gliclazide (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.

CONTRAINDICATIONS

Contraindications to gliclazide include :

1. Known hypersensitivity or allergy to gliclazide
2. Unstable and/or insulin dependent diabetes mellitus, ketoacidosis, coma
3. During stress conditions such as serious infection, trauma, or surgery
4. Liver disease or renal impairment
5. Pregnancy.

WARNINGS

The use of Rhoxal-gliclazide (gliclazide) will not prevent the development of complications peculiar to diabetes mellitus.

Use of Rhoxal-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 due to worsening of their diabetic state. If a loss of adequate blood glucose-lowering response to Rhoxal-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 sulphonylureas 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 interactions, hypoglycemia may be potentiated when a sulfonylurea is used concurrently with agents such as: long-acting sulfonamides, tuberculostatics, phenylbutazone, clofibrate, monamine 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 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 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.

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:

Rare cases of jaundice have been reported.

Dermatological reactions:

Allergic reactions (pruritus, erythema, urticaria and morbilliform or maculopapular rash) have been reported. Treatment must be interrupted if these persist. Cutanea porphyria tarda and photosensitivity have been described with sulfonylurea drugs.

Hematological reactions:

As with all 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 sulfonylureas. Clinical experience to date has shown that gliclazide has a low incidence of disulfiram type reactions.

Endocrine reactions:

A decrease in 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 sulphonylureas. 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 sulphonylureas 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 sulphonylureas 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 hypoglycemia 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 gliclazide or any other hypoglycemic agent. Determination of the proper dosage for gliclazide for each patient should be made on the basis for frequent determinations of blood glucose during dose titration and throughout maintenance.

The recommended daily dosage of Rhoxal-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. Rhoxal-gliclazide should be taken preferentially with meals.

The recommended starting dose of Rhoxal-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 drugs 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 decomposition and whose insulin requirements are less than 40 units per day may be considered for Rhoxal-gliclazide therapy.

If a change from insulin to Rhoxal-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.

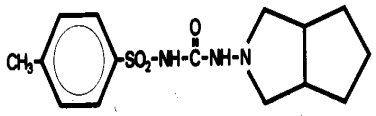
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name : gliclazide

Chemical Name : 1-(2-azabicyclo[3.3.0]oct-3-yl)-3-p-tolylsulphonylurea

Structural Formula :



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

Molecular Weight : 323.41

Description : Gliclazide is a white, crystalline, odourless powder.

Solubility : Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone, slightly soluble in ethanol (96%)

pKa : 5.8

Melting point : 165 to 170 ˚C

Composition

Non-medicinal ingredients: Lactose, Magnesium Stearate, Microcrystalline Cellulose, Povidone, Sodium Starch Glycollate and Talc.

Stability and Storage Recommendations

Store at room temperature between 15 to 30˚C.

AVAILABILITY OF DOSAGE FORM

Rhoxal-gliclazide (gliclazide) is available as 80 mg white, flat bevelled edged tablet with "GZ80" on one side and quadrisect scored on the other side.

Rhoxal-gliclazide is available in blister packs containing 20 and 60 tablets and white opaque HDPE bottles of 20, 60, 100 and 500 tablets.

INFORMATION FOR THE CONSUMER

The product monograph is available to physicians and pharmacists on request.

Rhoxal-gliclazide (gliclazide) is a product of **Rhoxalpharma Inc**.

Rhoxal-gliclazide is available only with a physician's prescription. It belongs to the family of hypoglycemic (antidiabetic) medicines which are taken orally to help reduce the amount of sugar in the blood. It is to be used together with a medically recommended 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 discuss the benefit of the medicine as well as the risks of using it. You should also find out about alternate ways to control your diabetes such as by diet alone or by diet plus insulin.

Use only as directed. Do not change 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 possible treatment for your medical problem, your physician should be told if:

- you have taken gliclazide or any other anti-diabetic medicine and if you have developed an allergy or any tolerance to it or to sulfonamide (sulfa) medications, including thiazide diuretics.
- you suffer from any other conditions, in particular kidney or liver disease.
- you are pregnant or intend to become pregnant or are breast feeding or intend to breast feed.
- you are taking any other medications with or without a prescription.

Proper use of this medicine

Follow carefully the special meal plan as recommended by your doctor. This is the most important part of controlling your condition and is necessary if the medicine is to work properly.

Take Rhoxal-gliclazide with meals as directed by your physician. Do not take more or less of it than your doctor recommended, and take it at the same time each day. If you miss a dose of Rhoxal-gliclazide, 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. Doses must not be doubled up.

Rhoxal-gliclazide is contraindicated (must not be taken) during pregnancy.

The safety of Rhoxal-gliclazide in adolescents and children has not been established.

Rhoxal-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 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 start taking this medicine.

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

Do not take any other medicine, unless it is prescribed or approved

by your doctor. If you require medical assistance, inform the medical practitioner that you are taking Rhoxal-gliclazide.

Avoid drinking alcoholic beverages until you have discussed their use with your doctor. Some patients who drink 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 your blood sugar levels (hypoglycemia).

Notify your physician about any illness which may develop during your treatment with Rhoxal-gliclazide and about any prescribed or non-prescribed medication you may be taking.

Side effects of this medicine

Along with their needed effects, oral antidiabetes medications may cause some unwanted effects. The more frequent side effects noticed during clinical trials with gliclazide were hypoglycemia (low blood sugar) and indigestion or stomach upsets.

You should be aware 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, sugar cubes or table sugar (dissolved in water).

Allergic reactions to this medicine are rare; however, if you suspect these consult your doctor.

Additional information on Rhoxal-gliclazide may be obtained from your physician or pharmacist.

PHARMACOLOGY

HUMAN PHARMACOLOGY

1. Pharmacokinetics and Metabolism

Absorption: Gliclazide is extensively absorbed from the gastrointestinal tract. Following oral administration of 80 mg/kg to 13 healthy subjects, the peak plasma level of 3.9 µg/mL was attained within 4 hours in 7 subjects. In another study, following oral doses of 40 or 80 mg to healthy volunteers, diabetic patients, and non-diabetic patients, absorption was similar in all groups with peak drug levels of approximately 3.5 µg/mL occurring within 4 hours.

Distribution: The mean apparent volume of distribution in four healthy subjects was 20 to 40% of body weight which suggests only limited tissue distribution.

Protein binding: In 15 subjects, 85-97% of the drug was bound to protein, but there was considerable variability in the extent of binding. At therapeutic levels, the protein binding of the drug was 93%.

Metabolism: Gliclazide is extensively metabolized, less than 20% of the dose being excreted unchanged in the urine. However, in

plasma, gliclazide represents over 90% of all drug-related material, the most important metabolite (an N-oxygenated derivative) being present only to the extent of 1%. As with other sulphonylureas, gliclazide is oxidized to produce either hyroxylated metabolites or N-oxygenated compounds, and the corresponding alcohol and carboxylic acid.

Excretion: Gliclazide is essentially eliminated via the urine; 60 to 70% as against 10 to 20% via feces. When the pharmacokinetics of gliclazide in diabetic and non-diabetic patients with varying degrees of renal dysfunction was compared with that of healthy volunteers, it was found that absorption was similar in all groups and there were no differences in other pharmacokinetic parameters suggesting that, in general, dosage alterations are not required in renal failure.

No significant differences in pharmacokinetic parameters were seen between single doses in healthy (40 mg/day) and diabetic subjects (80 mg/day) or after repeated (for 7 days) dosing.

2. Pharmacodynamics

In 12 healthy subjects, 200 mg gliclazide lowered the blood glucose

levels to a significantly greater extent than 2000 mg of tolbutamide at 2 and 3 hours after administration of the drug.

In 23 healthy subjects, administration of single oral doses of 80 mg gliclazide produced a maximum reduction of 20% in blood glucose levels after 2 hours, the levels returning to control values 4 to 6 hours after administration of the drug.

Patients with maturity onset diabetes mellitus, at doses ranging from 40 to 320 mg, have shown to lower hyperglycemia in response to oral and intravenous glucose, a standard meal, after food given at 4 and 11 hours after drug administration and during an arginine tolerance test.

In patients with moderate non-insulin-dependent diabetes, gliclazide significantly decreased fasting plasma glucose levels (87 ± 6 vs 110 ± 4 in controls; $p < 0.01$) without detectable increase in basal insulin levels or insulin-mediated glucose disposal, and in the absence of a significant increase in insulin binding to erythrocytes.

Therapy with gliclazide has produced decreases in plasma cholesterol, triglyceride and fatty acid levels, with at least one of the decreased levels reaching statistical significance.

When the metabolic and hemobiological properties of gliclazide and glibenclamide were compared, both drugs produced improvements in metabolic control as evidenced by the decrease in HbA_1 concentrations. In addition a significant fall in ADP-induced platelet aggregation was seen in those receiving gliclazide.

The changes in IRI, blood sugar and free fatty acids produced by gliclazide in diabetic patients were similar to those seen after therapy with tolbutamide and glibenclamide. However, the metabolic effects were more prolonged than those of glibenclamide.

ANIMAL PHARMACOLOGY

1. Pharmacokinetics and Metabolism

The pharmacokinetics of gliclazide was studied in the rat, rabbit, dog and monkey. Animals were fasted overnight and the drug was administered at 3 mg/kg for the dog and monkey and at 10 mg/kg for the rat and rabbit. The pharmacokinetic parameters are summarized below:

Table 1. Pharmacokinetic Parameters In Different Species

Species	No.of subjects	Single Oral Doses (mg/kg)	Absorption T 1/2(h)	Plasma Peak (h)	Volume of Distribution (% body weight)	Plasma Half-time (h)
Monkey	4	3 50	0.3 -	1-2 -	24.4 108	2.9 6.2
Beagle	3	3 50	0.7 -	2-6 -	21.3 22.0	10.1 9.9
Rabbit	5	10 25	0.7 -	3 -	30.8 51.8	3.9 5.9
Rat	5	10	0.5	1	53.8	2.5

Gliclazide was rapidly absorbed in all species, consistently reaching peak plasm levels within 2 to 3 hours. The apparent volume of distribution was fairly low (20-40%) and similar in all species indicating extensive protein binding (4). The protein binding was 94% in the monkey, 89% in the rabbit, and 87% in dog.

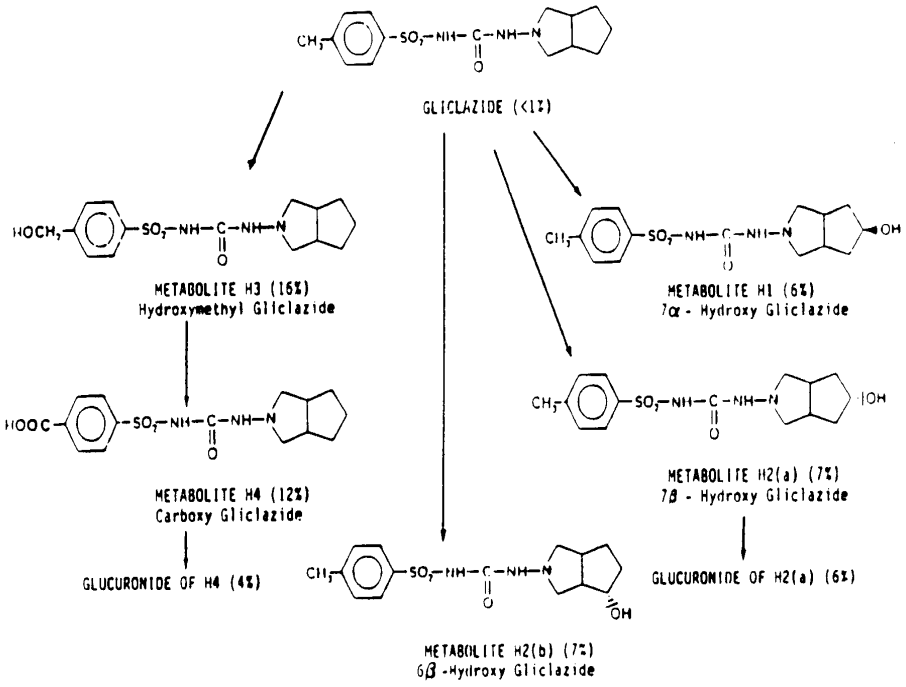
Plasma concentrations declined exponentially as a single phase. The elimination was longer (10.1 hr) in the dog while it was much faster (2.5 to 4 hr) in the monkey, rat and rabbit.

Gliclazide was extensively metabolized with less than 20% of the dose being excreted unchanged in the urine. The urinary metabolic profile indicated at least 8 metabolites in the dog, monkey, and rat with quantitative similarities and also quantitative differences. The

exception to this was for the two major metabolites (chloroform and ethylacetate) which represented a total of 30-40% of the dose in each animal. The principal metabolic pathways of gliclazide is shown below:

Studies with ^{14}C - gliclazide indicated that the elimination of the total drug and related materials into the urine and feces were similar for all species with 60-70% of the dose to be excreted in the urine and 10-20% in the feces.

The pharmacokinetics of gliclazide was studied following oral and



VALUES ARE APPROXIMATE % OF DOSE EXCRETED INTO 0-24 HOUR URINE

intravenous administration (30 mg/kg) to normal and analbuminemic rats. The plasma concentration of the drug in the mutant was much lower than that in the normal rats. The total body clearance and steady state volume of distribution of the drug was greater in analbuminemic rats than normal rats. Following a single oral dose, the liver displayed the highest radioactivity among all tissues. Following intravenous dosing, the biliary and urinary excretion rates of radioactivity were much greater in mutant than in normal rats.

2. Hypoglycemic Activity

The hypoglycemic action of gliclazide has been noted in the rat, rabbit, guineapig and dog following intravenous or oral administration. In rats and rabbits, this effect was dose dependent.

In rats, the hypoglycemic effect was dose-related following oral doses of 0, 2.5, 5, 10, or 50 mg/kg gliclazide with the maximum effect occurring 1-2 hours post dosing. The lower dose caused an initial hypoglycemia with a slight hyperglycemic effect within 24 hours. No differences were seen in the hypoglycemic effect between the 50 and 100 mg/kg doses.

Comparison of ED_{30} shows that gliclazide was nine times more

active than tolbutamide in the rabbit and 25 times more active in the rat. The duration of action of the gliclazide was also greater than that of tolbutamide. The ED_{50} was 3 mg/kg compared with 80 mg/kg for tolbutamide. In rabbits, gliclazide was 9 times more active than tolbutamide with an ED_{30} of 5.4 mg/kg compared with 38 mg/kg for 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.

When the hypoglycemic activity of gliclazide was investigated following oral administration to normal and analbuminemic rats, the drug exhibited a stronger hypoglycemic action in analbuminemic rats than in normal rats indicating that albumin plays an important

role in the hypoglycemic activity of the drug.

3. Hemovascular Activity

Oral or intravenous administration of gliclazide to rabbits and oral administration to dogs, resulted in significant decreases in platelet stickiness and to a certain extent inhibition of platelet aggregation. In addition, the drug exhibited some fibrinolytic 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.

Oral administration of gliclazide at 100 to 300 mg/kg to streptozotocin-diabetic rats restored the reduced formation of prostaglandin I_2 formation.

The effect of gliclazide on prostaglandin and thromboxane synthesis was studied in guineapig platelets both in *ex vivo* and *in vitro*. Gliclazide caused inhibition of arachidonate release from platelet phospholipids both *ex vivo* and in vitro.

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

The effectiveness of gliclazide in preventing thrombosis in capillaries affected by vascular complications of diabetes was studied in diabetes-induced rats. Gliclazide showed some unusual beneficial properties involved in the evolution of the microvascular complications in diabetic patients.

TOXICOLOGY

Acute Toxicity

Species/ Strain	Mean Weight (g)	No.of Animals	LD_{50} (mg/kg)
Mouse/CD	25	10 M & 10 F	>3000
Mouse/ ICR	20	10 M & 10 F	>4000
Rat/ SD	250	10 M 10 F	3733 3407
Rat/ CPY	110	6 M & 6 F	>4000
Guinea pig	240	4 M	48 hr: 1732 10 days: 1599
		4 F	48 hr: 2244 10 days: 2068
Dog/Beagle	7 kg	3 M & 3 F	>3000

The LD_{50} was 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 was essentially linked to the hypoglycemic effect of the drug.

Subchronic Toxicity

Groups of two male and two female beagle dogs were given oral administration of gliclazide at doses of 0, 15, 30, 45, or 90 mg/kg/day for 30 days. Mortality occurred in two dogs at the 90 mg/kg/day dose due to prolonged hypoglycemic coma following two weeks of treatment. Except for an increase in liver weight no other

toxicity was seen. Except for a decrease in blood glucose, no changes were seen in hematology, clinical chemistry, or histopathology.

Groups of five male and five female guinea pigs were treated with gliclazide at doses of 0, 25, 50, or 100 mg/kg/day, 6 days per week for two months. Only male pigs at the 50 mg/kg/day dose group showed delayed weight gain. All others had normal biochemical, hematological and histopathological results.

Chronic Toxicity

In a 6-month oral toxicity study, groups of 10 male and 10 female Sprague-Dawley rats were administered gliclazide at doses of 0, 25, 100, or 200 mg/kg/day, 6 days/week for six months.

Male rats at 100 mg/kg/day group showed significant decreases in blood urea and blood glucose. Liver and kidney weights were increased in male rats, but the increase was not accompanied by any histopathological changes in these tissues.

In a study conducted in Japan, higher doses of gliclazide (50, 100, 200, 400 and 800 mg/kg) induced slight increases in liver enzymes together with slight decreases in erythrocytes counts, hematocrit

values and hemoglobin concentration in females at doses of 200 mg/kg and higher.

Groups of three male and three female beagle dogs were treated for six months with 15 or 30 mg/kg of gliclazide or 50 mg/kg of tolbutamide. In the gliclazide group, mortality occurred in one dog at 15 mg/kg and in two dogs at 30 mg/kg due to hypoglycemic coma. In the tolbutamide group, one dog exhibited convulsions and four dogs showed severe gastrointestinal disturbances. Body weight changes and food consumption were similar in both drug groups. Dogs receiving gliclazide had a 40% fall in blood glucose levels while signs of hepatotoxicity were seen in those receiving tolbutamide.

Histopathology revealed increase in weight of the liver in the dogs that died in the gliclazide group. Increase in the weight of the liver and lesions of toxic hepatitis were seen in 5 of 6 dogs in the tol-butamide group.

In a 1-year oral toxicity study, groups of four male and four female dogs were treated with gliclazide at 0, 12, or 24 mg/kg/day for 12 months; 4 dogs/dose level were sacrificed after 90 days. No mortality occurred during the study. There were no significant

modifications in behavior or body weight gain. Toxic signs observed were significant fall in blood glucose and fluctuations in certain parameters (liver enzymes, lipid profile, creatinine). Necropsy showed swelling of the renal and hepatic parenchyma and at the highest dose a slight increase in the weight of the thyroid and slight decease in the weight of the pituitary gland.

In a 12-month study, groups of four male and four female rhesus monkeys were given oral doses of gliclazide at 0, 20, 60 or 180 mg/kg. No significant treatment-related changes were observed in clinical conditions, body weight, food or fluid intake, laboratory values, ophthalmology, or histopathology.

TERATOGENICITY

Groups of 30 female CD/SPF mice were given oral administration of gliclazide at doses of 0, 50, 200, or 500 mg/kg/day starting from mating and throughout gestation. Gliclazide was not teratogenic; treatment did not modify fertilization and abortion rates.

Groups of 20 female CFY-SPF rats were given oral administration of gliclazide at doses of 0, 50, 100, or 200 mg/kg/day from day 6 through 15 of gestation. No teratogenicity was seen.

In another study, groups of 60 female SD/SPF rats were given oral administration of gliclazide at doses of 0, 15, 30, 60, 120, 240, or 480 mg/kg/day throughout gestation. Treatment 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.

In groups of 15 female rabbits, administration of gliclazide at doses of 0, 10, 25, or 50 mg/kg/day during gestation days 6 through 18 induced no effect on the number of fetal resorption, percentage of abortions nor the mean number of fetuses per litter.

In another rabbit study, groups of 6 female New Zealand White rabbits were given doses of 0, 50, 75, 100 or 200 mg gliclazide/kg/day for 13 days and the animals were observed for 8 days. Maternal toxicity and embryotoxicity were characterized by gastrointestinal and renal lesions accompanied by anorexia and weight loss. There was no evidence of a teratogenic effect.

FERTILITY AND REPRODUCTION

Male and female SD rats received gliclazide at doses of 0, 10, 50, or 200 mg/kg/day; males were treated for 8 weeks prior to mating and until 15 days after littering, and the females were treated for 70

days before mating and until weaning. There was no evidence of any change in fertilization nor abortion rates.

Treatment had no adverse effects on fetal resorption, placental hemorrhage and fetal atrophy rates. The genital tract of treated parents showed no abnormality imputable to treatment.

No embryotoxicity was seen in the fetus of females sacrificed before littering. A significant decrease in the viability of offspring was seen at 48 hours in females in which gestation was allowed to run to term. 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 evaluated for gene mutation in the Ames assay and for chromosomal aberrations both *in vivo* and *in vitro*.

Gene Mutation Tests

In one assay, gliclazide was tested at concentrations of 0, 0.005, 0.01, 0.05, 0.1, 0.5, 1. 3, 5, or 8 µg/plate in *Salmonella typhimurium* strains TA 98, TA100, TA 1535, TA1537, and TA1538 both with and without metabolic activation. There was no evidence of mutagenic

effect.

In a second assay, gliclazide was tested at concentrations of 0, 0.05, 0.1, 0.5, 1, 3, 5 or 8 µg/plate in *Salmonella typhimurium* strains TA 97, TA 98, TA100, TA102, TA 1535, TA 1537, and TA 1538 both with and without metabolic activation. There was no evidence of a mutagenic effect.

In Vitro Chromosomal Aberration Assay

Gliclazide was not clastogenic when tested in an *in vitro* chromosomal assay using human lymphocytes. The concentrations were 0, 0.003, 0.01, or 0.033 mg/mL with metabolic activation and 0, 0.01, 0.033, or 0.1 mg/mL without metabolic activation. Cyclophosphamide (0.02 mg/mL) and bleomycin (0.250 mg/mL) were used as positive controls with and without metabolic activation.

In Vivo Chromosomal Aberration Assay

In an *in vivo* micronucleus assay, groups of 10 CF-1 mice were treated with a low dose (1 g/kg x 2) and a high dose (2 g/kg x 2) of gliclazide; a group of 10 mice served as negative controls while another group of 5 mice received cyclophosphamide (50 mg/kg x 2) as the positive control.

There was no evidence of mutagenicity; no significant variations were seen in the number of erythrocyte micronuclei.

In a second micronucleus test with SPF Swiss mice the following protocol was used:

- 24 mice for the preliminary toxicology test that 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 toxicity 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 mice.

CARCINOGENICITY

Although specific carcinogenicity studies have not been performed with gliclazide; no evidence of carcinogenicity was seen in chronic

toxicity studies in rats, dogs, and monkeys. In addition, gliclazide was not mutagenic both in *in vivo* and *in vitro*.

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