

PRODUCT MONOGRAPH

Pr **DIAMICRON**[®]

Gliclazide 80 mg tablets

Hypoglycemic sulfonylurea
Oral hypoglycemic agent

SERVIER CANADA Inc.
235 Boulevard Armand Frappier
Laval, Quebec H7V 4A7

Date of Approval:
December, 1989

Date of Revision:
July 13, 2016

Control No. 193245

PRODUCT MONOGRAPH

DIAMICRON®

Gliclazide 80 mg tablets

Oral hypoglycemic agent

ACTIONS AND CLINICAL PHARMACOLOGY

DIAMICRON® (gliclazide) is a hypoglycemic agent of the sulfonylurea group.

The hypoglycemic action of DIAMICRON® (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 DIAMICRON® (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.

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 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 DIAMICRON[®] (gliclazide) will not prevent the development of complications peculiar to diabetes mellitus.

Use of DIAMICRON[®] (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 DIAMICRON[®] (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 & Drug-Herb Interactions](#)). Under these conditions, discontinuation of DIAMICRON[®] (gliclazide) and administration of insulin should be considered.

Hematologic

Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD)-deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since DIAMICRON[®] 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 DIAMICRON[®] 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, DIAMICRON[®] is contraindicated in patients with severe hepatic impairment ([See CONTRAINDICATIONS](#) and [PRECAUTIONS, Monitoring and Laboratory Tests](#)).

Renal

The metabolism and excretion of sulfonylureas including DIAMICRON[®] 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, DIAMICRON[®] is contraindicated in patients with severe renal impairment ([See CONTRAINDICATIONS](#) and [PRECAUTIONS, Monitoring and Laboratory Tests](#)).

Peri-Operative Considerations

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

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 DIAMICRON® 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 DIAMICRON®, 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](#)).

Skin

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

Special Populations

Pregnant Women

Gliclazide is contraindicated in pregnancy. It is recommended that insulin be used during pregnancy in diabetic women ([see CONTRAINDICATIONS](#)).

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

Nursing mothers

The product is contra-indicated in breast-feeding mothers. Some sulphonylurea drugs are excreted in human milk although it is not known whether DIAMICRON® (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. DIAMICRON® is therefore not recommended for use in children and adolescents.

Geriatrics

Efficacy and tolerance of DIAMICRON®, prescribed using the same therapeutic regimen in subjects over 65 years, has been confirmed in clinical trials.

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

Monitoring and Laboratory Tests

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

Blood glucose control in a patient receiving DIAMICRON® 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.

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

Certain drugs tend to induce hyperglycemia and may lead to loss of 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.

Combination with anticoagulant therapy (warfarin and other) must be taken into account because sulfonulureas 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 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.

Drug-Herb Interactions

St. John's Wort

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

ADVERSE REACTIONS

In clinical trials involving about 2000 patients treated with DIAMICRON[®] (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 post-market 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 phosphatase) 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 DIAMICRON® (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 DIAMICRON® (gliclazide) during a study involving 15 patients.

Laboratory tests:

The pattern of laboratory tests abnormalities observed with DIAMICRON® (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 and toxic epidermal necrolysis) 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 phosphatase); isolated cases of impairment of liver function with cholestasis and jaundice which can regress after withdrawal of the drug or may lead to life-threatening liver failure. Discontinue treatment if cholestatic jaundice appears.

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 DIAMICRON[®] (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 DIAMICRON[®] (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. DIAMICRON[®] should be taken preferentially with meals.

The recommended starting dose of DIAMICRON[®] (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 DIAMICRON[®] (gliclazide) therapy after cessation of insulin. If a change from insulin to DIAMICRON[®] (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

Scored, white tablets, breakable into four, each containing 80 mg of gliclazide.

INFORMATION TO THE PATIENT

Full prescribing information is available to the physicians and pharmacists.

DIAMICRON[®] is the trademark of SERVIER CANADA for gliclazide.

DIAMICRON[®] is available only with your physician's prescription.

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

DIAMICRON[®] 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

DIAMICRON[®] 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 DIAMICRON[®] 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.

DIAMICRON[®] 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 DIAMICRON[®] 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.

DIAMICRON[®] 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 DIAMICRON[®] in adolescents and children has not been established.

DIAMICRON[®] 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 DIAMICRON[®].

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

Herbs that may interact with DIAMICRON[®] 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, 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 DIAMICRON®. 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 DIAMICRON® as it can lead to drop in blood sugar (hypoglycemia).

Inform your physician about any illness which may develop during your treatment with DIAMICRON® 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 DIAMICRON® 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, 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 DIAMICRON®. 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.

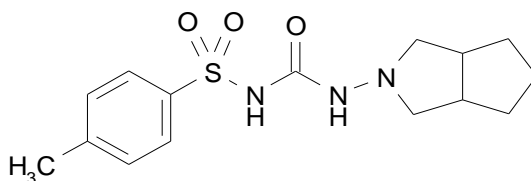
Additional information on DIAMICRON® may be obtained from your physician or pharmacist.

PHARMACEUTICAL INFORMATION

1) Active principle:

Trade mark: Diamicon®

- International non-proprietary name: gliclazide
- Chemical name:
1-(3-Azabicyclo[3.3.0] -oct-3-yl)-3-(p-tolylsulfonyl)urea
- Chemical structure:



- Molecular weight: 323.42
- Description:

Physical form: white, crystalline, virtually odorless powder.

Solubility:

- practically insoluble in water
- free soluble in chloroform
- sparingly soluble in acetone

Acid function 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°

2) Composition:

Unit formula:

active principle: 80 mg Gliclazide

excipients: lactose
corn starch
pregelatinized corn starch
magnesium stearate
talc
q.s. one finished 160.0 mg tablet

3) Stability and storage recommendations:

No special conditions

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 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 µm/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. Sulphonylurea 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 and 50 mg/kg	0.3 (1)	1-2 (1)	24.4 (1)	108 (4)	2.9 (1)	6.2 (4)
Beagle	3 3 and 50 mg/kg	0.7 (1)	2-6 (1)	21.3 (1)	22 (4)	10.7 (1)	9.9 (4)
Rabbit	5 10 and 25 mg/kg	0.7 (2)	3 (2)	30.8 (2)	51.8 (3)	3.9 (2)	5.9 (3)
Rat	5 10 mg/kg	0.5 (2)	1 (2)	53.8 (2)	-	2.5 (2)	-

(1) = 3 mg/kg PO

(3) = 25 mg/kg PO

(2) = 10 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).

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

3. Haemovascular activity

DIAMICRON® (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, DIAMICRON® (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 PGI₂ 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 nernous 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	DL 50 (mg/kg)	
Mouse CD-SPF	25 g	10 M	> 3 000	
		10 F		
Mouse ICR-HAN	20 g	10 M	> 4 000	
		10 F		
Rat SD-SPF	250 g	10 M	3733	5200 2679
		10 F	3407	5467 2123
Rat CFY	110 g	6 M	> 4 000	
		6 F		
Tricolor			48 hours	10 days

Guinea Pig	240 g	4 M	1732	1999	1599	2016
				1501		1269
		4 F	2244	2509	2068	2553
				1944		1675
Beagle dog	7 kg	3 M	> 3000			
		3 F				

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 hispathological 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 occurred as a result of technical problems.

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

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

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

- DIAMICRON[®] (gliclazide) belongs to the chemical class of the phenylsulfonyleurea which did not demonstrate any mutagenic or carcinogenic potential. Its metabolic pathway is consistent with the general metabolic pathway of the class.
- DIAMICRON[®] (gliclazide) was not associated with any mutagenic action in the numerous studies performed.
- Long term toxicity studies did not reveal any evidence of carcinogenicity.

- DIAMICRON® (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.

REFERENCES

- 1 Baba S et coll:
Double-blind randomized control study with gliclazide
Clin Eva 1983; **11**(1):51-94
- 2 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
- 3 Campbell DB, Forette B, Rolland A, Hopkins Y, Gordon BH:
Gliclazide pharmacokinetics in the elderly
Excerpta Medica 1982; **577**:8
- 4 Chan TK, Ckan V, Teng CS, Yeung RTT:
Progression of diabetic background retinopathy: the effect of gliclazide compared to glibenclamide and the relationship to haemobiological changes
Excerpta Medica 1982; **577**:7
- 5 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
- 6 Chiasson JL, Bergman RN, Verdy M, Hamet P, De Lean A:
Study on effect of gliclazide on secretion and action of insulin in normal and type II diabetic humans
Bull Int Diabete Fed 1987; **32**(1):9-11
- 7 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
- 8 Duhault J, Lebon F:
Protective activity of S 1702 on the microvascular system in normal and diabetic rats
Arzneimittelforsch 1972; **22**:1686-1690
- 9 Duhault J, Regnault F, Boulanger M, Tisserand F:
Prevention of experimental obstructions in the retinal microcirculation
Ophthalmologica 1975; **170**:345-352
- 10 Futijani B, Maeda J, Tsuboi T et coll:
Effect of gliclazide on prostaglandin I₂ formation in normal streptozotocin-induced diabetic animals
Jpn J Pharmacol 1983; **33**:965-970

- 11 Gamstedt A, Fagerberg SE:
Long-term metabolic effects of gliclazide in NIDDM
FADL Publish 1987; 16-19
- 12 Golay A, Broquet C, Chabot V, Studer S, Felber JP:
Effets métaboliques du gliclazide chez le diabétique de type II. Étude par calorimétrie indirecte
Schweiz Med Wochenschr 1984; **114**(8):261-264
- 13 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
- 14 Hoich RI, Ng FM:
Insulin-potentiating action of gliclazide (Diamicron)
Pharmacol Res Commun 1986; **18**(5):419-430
- 15 Holmes B et coll:
Gliclazide. A preliminary review of its pharmacodynamic properties and therapeutic efficacy in diabetes mellitus
Drugs 1984; **27**:301-327
- 16 Ings RMJ, Campbell B, Gordon BH, Beaufils M, Meyrier A, Jones R:
The effet of renal disease on the pharmacokinetics of gliclazide in diabetic patients
Br J Clin Pharmacol 1986; **21**(5):572-573
- 17 Jerums G et coll:
Lack of effect of gliclazide on early diabetic nephropathy and retinopathy: a two-year controlled study
Diabetes Res Clin Pract 1987; **3**:71-80
- 18 Kilo C, Dudley J, Kalb E:
Evaluation of safety and efficacy of gliclazide in non-insulin-dependent diabetic patients
Bull Int Diabete Fed 1987; **32**(1):27-29
- 19 Kosaka K et coll:
Clinical comparative study on the therapeutic effects of oral hypoglycaemic agents in patients with diabetic retinopathy
J Jpn Diab Soc 1983; **26**(5):531-540
- 20 Kuwashima J et coll:
Inhibition by gliclazide of platelet adhesiveness and aggregation in the rabbit made diabetic by alloxan
Yakugaku Zasshi 1979; **99**(1):50-64
- 21 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
- 22 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
 - 23 Marchand D et coll:
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
 - 24 Masbernard A, Portal A:
Le vrai problème du diabète. Essai du gliclazide, molécule originale à propriétés métaboliques et vasculaires
Sem Hop Paris Ther 1972; **48**(9):569-573
 - 25 Matsuoka N et coll:
Acute, subacute and chronic toxicity studies on gliclazide, a new sulfonylurea derivative
Jpn Pharmacol Ther 1980; **8**(8):41-69
 - 26 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
 - 27 Regnault F:
Gliclazide in the treatment of diabetic retinopathy
Adv Exp Med Biol 1979; **119**:443-448
 - 28 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; sous presse
 - 29 Shimizu M, Tsuboi J, Fujitani B et coll:
Pharmacological studies on gliclazide. Effects of gliclazide on platelet aggregation, adhesion and blood coagulation
Pharmacometrics 1976; **12**(2):295-302
 - 30 Tourniaire J, Orgiazzi J:
Gliclazide and thyroid function, an experimental and clinical study
Royal Soc Med Int Congr Symp 1980:151-155
 - 31 Tsuboi T, Fujitani B, Maeda J et coll:
Effect of gliclazide on prostaglandin and thromboxane synthesis in guinea pig platelets
Thromb Res 1981; **21**:103-110

- 32 Turner RC, Hoskerj P, Rudenski AS, Burnett MA, Matthews DR:
Similar reduction of first and second phase B-cell responses at three different glucose
levels in type II diabetes, and the effect of gliclazide therapy
Metabolism 1989; **38**(5):107-110