PRODUCT MONOGRAPH

NTP-GLYBURIDE

(glyburide)

Manufacturer's Standard

2.5 and 5 mg Tablets

Oral Hypoglycemic

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Glyburide

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 2.5 mg, 5 mg	Lactose monohydrate *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

NTP-GLYBURIDE (glyburide) is indicated:

NTP-GLYBURIDE (glyburide) is indicated as an adjunct to proper dietary management, exercise and weight reduction to lower blood glucose in adult patients with type 2 diabetes whose hyperglycemia cannot be controlled by diet and exercise alone or when insulin therapy is not required.

Pediatrics (<18 years of age)
Safety and effectiveness of glyburide has not been established. Use in patients under 18 years of age is not recommended (see WARNING AND PRECAUTIONS, Special Populations).

Geriatrics
Elderly with type 2 diabetes when treated with NTP-GLYBURIDE (glyburide) are more prone to hypoglycemia (see WARNINGS AND PRECAUTIONS, Special Populations).

CONTRAINDICATIONS

NTP-GLYBURIDE (glyburide) is contraindicated in patients with

- Known hypersensitivity or allergy to any sulfonylurea or sulfonamides or any other component of the formulation. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- Patients with Type 1 diabetes (formerly known as insulin-dependent diabetes mellitus or IDDM).
- Diabetic ketoacidosis with or without coma. This condition should be treated with insulin.
- Diabetic precoma or coma.
- During stress conditions such as severe infections, trauma or surgery.
- In the presence of liver disease or frank jaundice; or renal impairment.
- Patients treated with bosentan.
- Pregnancy and lactation.
  During pregnancy, no oral antidiabetic agent should be given.
  Due to the possible excretion in human milk, the patient should discontinue nursing or discontinue taking the drug depending on the importance of the drug to the mother. If glyburide is discontinued, the patient should be transferred to insulin therapy.

WARNINGS AND PRECAUTIONS

General

Use of NTP-GLYBURIDE must be viewed by both the physician and patient as a treatment in addition to diet and exercise and not as a substitute for proper dietary management, exercise and weight reduction or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet and exercise alone may be transient, thus requiring only short-term administration of NTP-GLYBURIDE. As is necessary during treatment with any blood-glucose-lowering drug, the patient and the physician must be aware of the risk of hypoglycemia.

In initiating treatment for type 2 diabetes, non-pharmacologic therapy (proper dietary management, exercise and weight reduction) should be emphasized as the initial form of treatment. Caloric restriction, weight loss and exercise are essential in the obese diabetic patient. Proper dietary management and exercise alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. If non-pharmacologic therapy fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea should be considered.

Patient Selection and Follow-Up

Careful selection of patients is important. It is recommended that response to sulfonylurea be measured as increased C-peptide. Those patients who do not respond with increased C-peptide will be less likely to show improvement.

It is imperative that there be careful ongoing attention to diet, adherence to regular exercise, reduction of body weight in obese patients, careful adjustment of dosage, instruction of the patient on hypoglycemic reactions and their control as well as regular, thorough follow-up examinations. Cardiovascular risk factors should be identified.

The effectiveness of any oral hypoglycemic drug, including NTP-GLYBURIDE, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be

due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon, known as secondary failure, is distinctive of primary failure in which the drug is ineffective in an individual patient when given for the first time.

Patients should therefore be monitored with regular clinical and laboratory evaluations, including blood glucose and glycosylated hemoglobin (AlC) determinations, to determine the minimum effective dosage and to detect primary failure (inadequate lowering of blood glucose concentrations at the maximum recommended dosage) or secondary failure (progressive deterioration in blood sugar control following an initial period of effectiveness). The rate of primary failure will vary greatly depending upon patient selection and adherence to diet and exercise. The etiology of secondary failure is multifactorial and may involve progressive β-cell failure as well as exogenous diabetogenic factors such as obesity, illness, drugs, or tachyphylaxis to the sulfonylurea.

Loss of control of blood glucose: If loss of adequate blood glucose lowering response to sulfonylurea is detected, treatment must be reassessed.

When a patient stabilized on any diabetic regimen is exposed to stress such as illness during therapy, fever, trauma, infection, or surgery, a loss of glycemic control may occur. At such times, it may be necessary to adjust the dosage of NTP-GLYBURIDE or consider discontinuation of NTP-GLYBURIDE and administration of insulin.

Hematologic
Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD)-deficiency with sulfonylurea agents can lead to hemolytic anemia. Since NTP-GLYBURIDE belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a nonsulfonylurea alternative should be considered.

Hypoglycemia
Hypoglycemia, sometimes prolonged and even life-threatening, may occur as a result of the blood-glucose-lowering action of NTP-GLYBURIDE. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Hepatic and/or renal disease, inadequate caloric intake, malnutrition and/or irregular meals, exercise without adequate caloric supplementation, debility, advanced age, patient non-compliance, when alcohol is ingested, certain disorders of thyroid function, adrenal or pituitary insufficiency, excessive glyburide dosage, treatment with glyburide in the absence of indication or concurrent use with other agents with blood glucose lowering potential (see Drug-Drug Interactions) may be predisposing factors. Oral hypoglycemic agents should be administered with caution to patients with Addison's disease.

The manifestations of hypoglycemia include: flushing or pallor, chilliness, excessive hunger, trembling, headache, dizziness, nausea, vomiting, restlessness, aggressiveness, depression, speech disorders, aphasia, sensory and/or visual disturbances, helplessness, lassitude, shallow respiration or bradycardia. In more severe cases, the clinical symptoms of a stroke or coma appear. However, symptoms of hypoglycemia are not necessarily as typical as described above and sulphonylureas may cause insidious development of symptoms mimicking cerebrovascular

insufficiency (e.g. disordered sleep, somnolence, impaired alertness and reactions, confusion, delirium, cerebral convulsions, paralytic symptoms or loss of consciousness).

Signs of adrenergic counter-regulation to hypoglycemia include: sweating, damp skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris, and cardiac arrhythmias. However, these symptoms may be milder or absent in patients who develop hypoglycemia gradually, patients with autonomic neuropathy, elderly or patients who receive concurrent treatment with sympatholytic agents (e.g. beta blockers, clonidine, reserpine, guanethidine) (see Drug-Drug Interactions).

Mild to moderate episodes of hypoglycemia can usually be treated with oral carbohydrates. Artificial sweeteners are ineffective in controlling hypoglycemia. The symptoms of hypoglycemia nearly always subside when hypoglycemia is corrected.

Severe hypoglycemia, which may be prolonged and has occasionally been life-threatening, may occur and mimics acute CNS disorders. Signs of severe hypoglycemia can include disorientation, loss of consciousness, and seizures. Severe hypoglycemia, or a protracted episode, which can only be temporarily controlled by usual amounts of sugar requires in-patient hospital care.

Cardiovascular
Some literature studies have suggested an association between the use of sulfonylureas and the risk of cardiovascular adverse events including cardiovascular mortality, since these agents may potentially impair cardioprotective processes. Although, there is inconsistency in the literature regarding a definite conclusion for this association, a cautious approach is nevertheless warranted. All patients on sulfonylureas, particularly high risk patients with cardiovascular disease, should be closely monitored for cardiovascular complications.

Hepatic
The metabolism and excretion of sulfonylureas including NTP-GLYBURIDE may be slowed in patients with impaired hepatic function (see Monitoring and Laboratory Tests below).

Renal
In patients with renal insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions.

Special Populations

Pregnant Women:
The use of NTP-GLYBURIDE is contraindicated for women planning a pregnancy (see CONTRAINDICATIONS). Recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Experts, including the Canadian Diabetes Association and the Canadian Medical Association recommend that insulin be used during pregnancy to maintain glucose levels as close to normal as possible.

Nursing women:
The use of NTP-GLYBURIDE is contraindicated in lactating women (see CONTRAINDICATION).

Pediatrics:
Safety and effectiveness of glyburide has not been established. Use in patients under 18 years of age is not recommended.

Geriatrics:
Elderly patients with type 2 diabetes are more susceptible to hypoglycemia.

Monitoring and Laboratory Tests
Fasting blood glucose should be monitored periodically to determine therapeutic response. Glycosylated hemoglobin (HbA1C) should also be monitored, usually every 3 to 6 months, to more precisely assess long-term glycemic control.

Hepatic function should be assessed before initiating therapy and periodically in patients with impaired hepatic function.

In patients with impaired renal function, blood and urine glucose should be regularly monitored. Elderly patients (malnourished, with impaired hepatic, renal, or adrenal function) will require periodic monitoring and special care.

Periodic assessment of cardiovascular, ophthalmic, hematologic, renal and hepatic status is recommended.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most commonly occurring significant adverse event of sulfonylureas (including glyburide) is hypoglycemia (see WARNINGS AND PRECAUTIONS).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Endocrine and Metabolism:

Reduced radioactive iodine uptake by the thyroid gland has been reported with oral hypoglycemic therapy.

Hepatic porphyria and disulfiram-like reactions have been observed in patients treated with oral hypoglycemic drugs. Elevation of liver enzyme levels has been reported very rarely in patients treated with glyburide. In isolated cases, impairment of liver function (e.g. cholestasis and jaundice) and hepatitis have been observed which can regress after withdrawal of the drug or may lead to life-threatening liver failure.

Cases of hyponatremia have been reported with sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increased release of antidiuretic hormones. Although there have been no reports for NTP-GLYBURIDE, the syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increased release of ADH.

Gastrointestinal: antidiuretic
Nausea, epigastric fullness and heartburn are common reactions. Vomiting, diarrhea, and abdominal pain have also been reported. These tend to be dose related and may disappear when dosage is reduced.

Hematologic:
Potentially life-threatening changes in the blood picture may occur. Rare cases of mild to severe thrombocytopenia which can manifest itself as purpura have been reported. Leukopenia, agranulocytosis, pancytopenia (which may be due to myelosuppression), erythrocytopenia, granulocytopenia, hemolytic anemia and aplastic anemia have been observed very rarely with glyburide therapy. These reactions may be reversible following discontinuation of the sulphonylurea antidiabetic agent.

Sensitivity/Resistance:
Allergic and pseudoallergic skin reactions such as pruritus, erythema, urticaria, morbilliform, or maculopapular eruptions have been reported in a number of patients. These may subside on continued use of glyburide, but if they persist the drug should be discontinued. Mild reactions such as urticaria may very rarely develop into serious and life-threatening reactions including dyspnea, hypotension or shock. Porphyria cutanea tarda and photosensitivity reactions have been associated with the use of oral hypoglycemic drugs. Allergic vasculitis have been observed very rarely in patients receiving glyburide and in some circumstances may be life-threatening.

Cross-sensitivity to sulfonamides or their derivatives may occur in patients treated with oral sulphonylurea hypoglycemic agents.

Other:
Transient visual disturbances may occur at the commencement of treatment due to fluctuations in blood glucose levels.

DRUG INTERACTIONS

Overview

Weakening of the blood-glucose-lowering effect and, thus, raised blood glucose levels may occur when taking other drugs.

Drug-Drug Interactions

Patients who receive or discontinue certain medications while undergoing treatment with NTP-GLYBURIDE may experience changes in blood glucose control.

Proper name	Reference	Effect	Clinical comment
ACE-inhibitors	T	The hypoglycaemic action of sulfonylureas may be potentiated.	When these drugs are administered to a patient receiving NTP-GLYBURIDE, the patient should be observed closely for hypoglycaemia. When these drugs are withdrawn from a patient receiving NTP-GLYBURIDE, the patient should be observed closely for loss of glycemic control.
Anabolic steroids and androgens	T		
Nonsteroidal anti-inflammatory drugs	T		
Salicylates	T		
Azapropazone	T		
Chloramphenicol	T		
Clarithromycin	C		
Fibrates (clofibrate)	T		
Coumarin derivatives	T		
Cyclophosphamide	T		
Disopyramide	T		
Fenyramidol	T		
Fenfluramine	T		
Fluconazole	T		
Fluoxetine	T		
Ifosfamide	T		
Miconazole	T		
Monoamine oxidase inhibitors	T		
Oxyphenbutazone	T		
Para-aminosalicylic acid	T		
Pentoxifylline (high dose parenteral),	T		
Phenylbutazone,	T		
Probenecid	T		
Propranolol	T		
Quinolones	T		
Sulfonamides (e.g sulphaphenazole)	T		
Sulphinpyrazone	T		
Sympatholytic agents (e.g. beta-blockers, guanethidine)	T		
Tetracyclines	T		
Tuberculostatics	T		
Acetazolamide,	T	These drugs tend to produce	When these drugs are

Barbiturates	T	hyperglycemia and may lead to loss of blood sugar control	administered to a patient receiving NTP-GLYBURIDE, the patient should be observed closely for loss of glycemic control. When these drugs are withdrawn from a patient receiving NTP-GLYBURIDE, the patient should be observed closely for hypoglycaemia.
Corticosteroids	T		
Diazoxide	T		
Diuretics (thiazides, furosemide)	T		
Proper name	**Reference**	**Effect**	**Clinical comment**
Epinephrine and other sympathomimetic agents	T		
Glucagon	T		
Laxatives (after protracted use)	T		
Isoniazid	T		
Nicotinic acid (in pharmacologic doses)	T		
Estrogen and progestogen	T		
Phenothiazines	T		
Phenytoin	T		
Rifampicin	T		
Thyroid products	T		
Sympatholytic drugs (such as beta-blockers, clonidine, guanethidine, and reserpine)	T		The signs of adrenergic counter-regulation to hypoglycemia may be reduced or absent in case of concomitant use with NTP-GLYBURIDE.
H2-receptor antagonists, betablockers, clonidine or reserpine	T		Concurrent use with NTP-GLYBURIDE may lead to either a potentiation or an attenuation of the blood-glucose-lowering effect
Barbiturates	T	Prolonged barbiturate action	To be used cautiously in patients receiving an oral hypoglycemic agent.
Coumarin derivatives	T	NTP-GLYBURIDE may potentiate or weaken the effects of coumarin derivatives.	
Cyclosporine	C	NTP-GLYBURIDE may increase cyclosporine plasma level, with potentially increased toxicity.	Monitoring and dosage adjustment of cyclosporin are recommended when both drug are coadministered.
Bosentan	C	An increased incidence of elevated liver enzymes was observed in patients receiving glyburide concomitantly with bosentan. Both glyburide and bosentan inhibit the bile salt export pump, leading to intracellular accumulation of cytotoxic bile salts.	This combination should not be used.

Drugs containing alcohol	C	Both acute and chronic alcohol intake may potentiate or weaken the blood-glucose-lowering action of NTP-GLYBURIDE in an unpredictable fashion.	Intolerance to alcohol (disulfiram-like reaction; flushing, sensation of warmth, giddiness, nausea, and occasionally tachycardia) may occur in patients treated with oral hypoglycemic drugs. Caution should be exercised with the concomitant use of alcohol-containing drugs.

Legend: C = case study; CT = Clinical Trial; T = Theoretical

In addition, the hypoglycaemic action of sulfonylureas is potentiated when used with insulin and other oral antidiabetics, which is not indicated.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Tests Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Alertness and reactions may be impaired due to hypo- or hyperglycemia, especially when beginning or after altering treatment, or when NTP-GLYBURIDE (glyburide) is not taken regularly. This may, for example, affect the ability to drive or to operate machinery.

Both acute and chronic alcohol intake may potentiate or weaken the blood-glucose-lowering action of glyburide in an unpredictable fashion. Intolerance to alcohol (disulfiram-like reaction: flushing, sensation of warmth, giddiness, nausea, and occasionally tachycardia) may occur in patients treated with oral hypoglycemic drugs. These reactions can be prevented by avoiding the use of alcohol.

DOSAGE AND ADMINISTRATION

Dosing Considerations

In diabetic subjects, there is no fixed dosage regimen for management of blood glucose levels. Individual determination of the minimum dose that will lower the blood glucose adequately should be made, aiming for glycemic targets as close to normal as possible and, in most people, as early as possible.

Over a period of time, patients may become progressively less responsive to therapy with oral hypoglycemic agents because of deterioration of their diabetic state. Patients should therefore be monitored with regular clinical and laboratory evaluations, including blood glucose and glycosylated hemoglobin (AlC) measurements, to determine the minimum effective dosage and to detect primary failure or secondary failure (see WARNINGS AND PRECAUTIONS).

Adjustment of glyburide dosage should be considered whenever factors predisposing the patient to the development of hypo- or hyperglycemia, such as illness, weight or life-style changes, are present (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS). As an improvement in control of diabetes is, in itself, associated with higher insulin sensitivity, glyburide requirements may fall as treatment proceeds. To avoid hypoglycemia, timely dose reduction or cessation of NTP-GLYBURIDE therapy must therefore be considered.

Recommended Dose and Dosage Adjustment

Newly-Diagnosed Diabetics
The initial dose is 5 mg daily (2.5 mg in patients over 60 years of age) administered with breakfast or a first meal and should be continued for 5 to 7 days. Depending on the response, the dosage should then be either increased or decreased by steps of 2.5 mg. The maximum daily dose of NTP-GLYBURIDE is 20 mg (higher doses normally have no additional effect on control of metabolic state). Occasionally, control is maintained with 2.5 mg daily. The majority of cases can be controlled by 5 to 10 mg (1 to 2 tablets) daily given as a single dose during or immediately after breakfast. Patients who eat only a light breakfast should defer the first dose of the day until lunchtime. If more than 10 mg (2 tablets) daily is required, the excess should be taken with the evening meal. It is very important not to skip meals after the tablets have been taken.

Changeover From Other Oral Hypoglycemic Agents
There is no exact dosage relationship between NTP-GLYBURIDE and other oral antidiabetic agents.
Discontinue previous oral medication and start NTP-GLYBURIDE 5 mg daily (2.5 mg in patients over 60 years of age). This also applies to patients changed over from the maximum dose of other oral antidiabetic medication. Determine maintenance dosage as in newly diagnosed diabetics.

Consideration must be given to the potency and duration of action of the previous antidiabetic agent. A break from medication may be required to avoid any summation of effects entailing a risk of hypoglycemia.

Changeover From Insulin
If a change from insulin to NTP-GLYBURIDE is contemplated in a patient with stable, mild, Type 2 diabetes, treatment with insulin should be discontinued for a period of two or three days to determine whether any therapy other than dietary regulation and exercise is needed. During this insulin-free interval, the patient's urine should be tested at least three times daily for glucose and ketone-bodies, and the results monitored carefully by a physician. The appearance of significant ketonuria accompanied by glucosuria within 12 - 24 hours after the withdrawal of

insulin strongly suggests that the patient is ketosis-prone and precludes the change from insulin to NTP-GLYBURIDE.

Missed Dose

The missed dose should be taken as soon as possible, unless it is almost time for the next dose. Mistakes, e.g. forgetting to take a dose, must never be corrected by subsequently taking a larger dose.

Measures for dealing with such mistakes (in particular forgetting a dose or skipping a meal) or in the event a dose cannot be taken at the prescribed time must be discussed and agreed between physician and patient beforehand.
If it is discovered that too high a dose or an extra dose of NTP-GLYBURIDE has been taken, a physician must be notified immediately.

OVERDOSAGE

Overdosage with sulfonylureas may result in hypoglycemia, but it should be noted that the dosage which causes hypoglycemia varies widely, and may be within the accepted therapeutic range in sensitive individuals.

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

The symptoms of hypoglycemia nearly always subside when blood glucose control is attained. However, some sulfonylurea-induced hypoglycemias may be refractory to treatment and susceptible to relapse, especially in elderly or malnourished patients. Patients must, therefore, remain under close observation. Continuous dextrose infusions for hours to days have been necessary.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Glyburide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which glyburide lowers blood glucose during long-term administration has not been clearly established.

With chronic administration in Type II diabetic patients, the blood glucose lowering effect persists despite a gradual decline in the insulin secretory response to the drug. Extrapancreatic effects may play a part in the mechanism of action of oral sulfonylurea hypoglycemic drugs. In addition to its blood glucose lowering actions, glyburide produces a mild diuresis by enhancement of renal free water clearance. Clinical experience to date indicates an extremely low incidence of disulfiram-like reactions in patients while taking NTP-GLYBURIDE.

Pharmacokinetics

Single-dose studies with glyburide in normal subjects demonstrate significant absorption within one hour, peak drug levels at about four hours, and low but detectable levels at twenty-four hours. Mean serum levels of glyburide, as reflected by areas under the serum concentrationtime curve, increase in proportion to corresponding increases in dose. Multiple-dose studies with glyburide in diabetic patients demonstrate drug level concentration-time curves similar to single dose studies, indicating no build-up of drug in tissue depots. The decrease of glyburide in the serum of normal healthy individuals is biphasic, the terminal half-life being about 10 hours. In single-dose studies in fasting normal subjects, the degree and duration of blood glucose lowering is proportional to the dose administered and to the area under the drug level concentration-time curve. The blood glucose lowering effect persists for 24 hours following single morning doses in non-fasting diabetic patients. Under conditions of repeated administration in diabetic patients, however, there is no reliable correlation between blood drug levels and fasting blood glucose levels. A one-year study of diabetic patients treated with glyburide showed no reliable correlation between administered dose and serum drug level.

The major metabolite of glyburide is the 4-trans-hydroxy derivative. A second metabolite, the 3-cis-hydroxy derivative, also occurs. These metabolites contribute no significant hypoglycemic action since they are only weakly active (1/400th and 1/40th, respectively, as glyburide) in rabbits.

Glyburide is excreted as metabolites in the bile and urine, approximately 50% by each route. This dual excretory pathway is qualitatively different from that of other sulfonylureas, which are excreted primarily in the urine.

Sulfonylurea drugs are extensively bound to serum proteins. Displacement from protein binding sites by other drugs may lead to enhanced hypoglycemic action. *In vitro*, the protein binding exhibited by glyburide is predominantly non-ionic, whereas that of other sulfonylureas (chlorpropamide, tolbutamide, tolazamide) is predominantly ionic. Acidic drugs such as phenylbutazone, warfarin, and salicylates displace the ionic-binding sulfonylureas from serum proteins to a far greater extent than the non-ionic binding NTP-GLYBURIDE. It has not been shown that this difference in protein binding will result in fewer drug-drug interactions with glyburide in clinical use.

STORAGE AND STABILITY

NTP-GLYBURIDE should be stored between 15 and 30ºC, and not beyond the expiry date indicated on the package.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NTP-GLYBURIDE (glyburide) 2.5 mg contains 2.5 mg glyburide. NTP-GLYBURIDE (glyburide) 5.0 mg contains 5.0 mg glyburide. Each tablet also contains as non-medicinal ingredients: colloidal anhydrous silica, lactose monohydrate, magnesium stearate, starch (corn starch and pregelatinized corn starch) and talc.

NTP-GLYBURIDE (glyburide) 2.5 mg tablets are compressed white, flat round beveled tablets with code letter “LB” above and “G” below the breakline on one side and plain on the other. Available in bottles of 100 and 500 tablets.

NTP-GLYBURIDE (glyburide) 5.0 mg tablets are white, biplane, oblong tablets with a score line on both sides, “LDI” is engraved on each side of the score-line and inverted. The other face is plain.

Available in bottles of 100 and 500 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

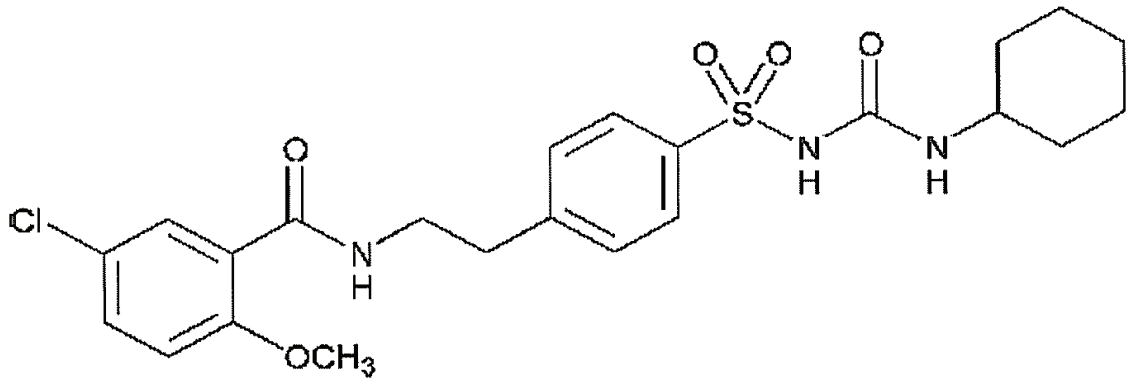
Proper name: Glyburide (as per USP), Glibenclamide (as per Ph. Eur.)

Chemical name: 1-[[4-[2-[(5-Chloro-2-methoxybenzoyl)amino]ethyl]phenyl]sulphonyl]-3-cyclohexylurea

Molecular formula: $C_{23}H_{28}ClN_3O_5S$

Molecular mass: 494

Structural formula:



Physicochemical properties: White or almost white, crystalline powder. Practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in alcohol and in methanol, with a melting range of 169 – 174 °C.

CLINICAL TRIALS

No clinical data available.

DETAILED PHARMACOLOGY

Animal
In the isolated, perfused rat pancreas, glyburide produced a sustained rise in insulin output. In the presence of 0.5 mcg/mL of glyburide, isolated rat pancreatic islets released insulin continuously[3]. When isolated pieces of rat pancreas were repeatedly exposed to glucose or glyburide for brief periods of time at intervals of 30 minutes, they consistently released insulin[3]. In the presence of 300 mg% of glucose, glyburide (2.5 mcg/min.) increased effectively insulin output from isolated rat pancreas[3,4].

Sirek et al.[13] found that the beta adrenergic blocker propranolol inhibits sulphonylurea-stimulated insulin secretion in the dog and that the hypoglycemia produced by glyburide in the presence of propranolol could be the result of extra-pancreatic effects.

TOXICOLOGY

The LD_{50} for white mice, rats and guinea pigs was found to be more than 15 g/kg body weight and for rabbits and beagles, more than 10 g/kg body weight when glyburide is given orally. The LD_{50} in rats following intraperitoneal injection is 6.3 to 8.4 g/kg body weight.

Long-term feeding experiments were carried out in rats and dogs over the course of one year. Rats were given glyburide in their food in doses of approximately 0.2, 1.0 and 5.0 mg/kg body weight daily. The highest dose is equivalent to 350 times the minimal hypoglycemic dose in man. Organ function tests were carried out continuously. Hematological examination, blood sugar tests and urinary analyses were performed every three months. None of the rats showed any abnormal findings in the function tests or the blood and urine studies. Subsequent post-mortem examination revealed no macroscopic or histological changes attributable to a toxic effect of glyburide.

Dogs were given glyburide by mouth at dose levels of 0.4, 2.0 and 10.0 mg/kg body weight daily. The highest dose is equivalent to 650 times the minimal effective hypoglycemic dose in man. Regular checks of blood cell counts, blood glucose, urine, electrolytes, electrophoresis, BUN and serum enzyme levels (GPT, GOT, LDH, AP) showed no abnormalities. All the animals behaved normally during the period of the experiment. There was no vomiting or diarrhea, and their weights remained unchanged. Subsequent post-mortem examination and histological investigations showed no abnormality.

Teratological tests were carried out in rats and rabbits. Rats were given 0.2, 20 and 2,000 mg/kg body weight of glyburide from day 7 to 16 of gestation. For rabbits the doses were 0.035, 3.5 and 350 mg/kg given from day 7 to 17 of gestation in a starch suspension by gastric tube.

Examination of the intact fetuses, followed by examination of transverse sections and of the stained skeleton, showed no evidence of teratogenic action.

REFERENCES

1. Blant L, Fabre J, Zahno GR. Comparison of the pharmacokinetics of Glipizide in Glipizide in Glibenclamide in man. Europ J Clin Pharmacol 1975;9:63-69.

2. Falko JM, Osei K. Combination insulin/glyburide therapy in Type II diabetes mellitus. Effects on lipoprotein metabolism and glucoregulation. The American Journal of Medicine. 1985 September 20;79 Suppl 3B:92-101.

3. Fucella ML, Tamassia V, Valzelli G. Metabolism and kinetics of the hypoglycemic agent Glipizide in man - comparison with Glibenclamide. J Clin Pharmacol. 1973;13:68-75.

4. Fussgaenger RD, Goberna R, Hinz M, Jaros P, Karsten C, Pfeiffer EF, Raptis S. Comparative studies of the dynamics of insulin secretion following HB 419 and tolbutamide of the perfused isolated rat pancreas and the perfused isolated pieces and islets of rat pancreas. Hormone and Metabolic Research. 1969;1 Suppl:34.

5. Grodsky GM, Curry D, Landahl H, Bennet L. Further studies on the dynamic aspects of insulin release *in-vitro* with evidence of a two-compartmental storage system. Acta Diabetological Latina 1969;6 Suppl 1:554.

6. Hajdu P, Kohler KF, Schmidt FH, Spingher H. Physikalisch-chemische und analytische Unter suchungen an HB 419. Arzneim Forsch 1969;19(suppl):1381-1386.

7. Hirn S, Konigstein RP. HB 419, ein neues orales Antidiabetikum und sein Anwendung in hohen Alter. Weiner Medizinische Wochenschrift 1969;111:632.

8. Karlander SG, Gutniak MKM, Efendic S. Effects of combination therapy with glyburide and insulin on serum lipid levels in NIDDM patients with secondary sulfonylurea failure. Diabetes Care. 1991 November;14(11):963-967

9. Mariani MM. The action of sulfonylureas on the insulin secretion of the perfused rat pancreas. Acta Diabetologica Latina 1969;6 Suppl 1:256.

10. Morris AD, Boyle D, McMahon AD, Pearce H, Evans J, Newton RW. ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. Diabetes Care. 1997 Sept; 20(9): 1363-7.

11. Raptis S, Rau RM, Schroeder KE, Faulhaber JD, Pfeiffer EF. Comparative study of insulin secretion following repeated administration of Glucose, Tolbutamide and Glibenclamide (HB 419) in diabetic and non-diabetic human subjects. Hormone and Metabolic Research 1969;1 Suppl:65.

12. Reich A, Abraira C, Lawrence AM. Combined Glyburide and insulin therapy in Type II diabetes. Diabetes Research 1987; 6: 99-104

13. Rupp W, Christ OE, Fuelberth W. Studies on the bioavailability of Glibenclamide. Arzneim Forsch 1972;22:47.

14. Rupp W. Bioequivalence study - Glyburide. (Dossier technique, Hoechst Pharmaceuticals, Département médical, Montréal, Qué.).

15. Rupp W. Dose-response study of the Hoechst formulation of Glyburide. (Dossier technique, Hoechst Pharmaceuticals, Département médical, Montréal, Qué.).

16. Schulz E, Schmidt FH. Uber den Einfluss von sulfaphenazol, phenylbutazon und phenprocumarol auf die Elimination von Glibenclamid beim Menschen. Verhandlunen deutsche Geselschaft fur innue Medizin 1970;76:435.

17. Sirek OV, Sirek A et Policova Z. Inhibition of sulphonylurea-stimulated insulin in secretion by beta adrenergic blockade. Diabetologia 1975;II(4):269.

18. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with Type 2 diabetes (UKPDS 33). The Lancet. 1998;352:837-853.

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

NTP-GLYBURIDE
Glyburide Tablets

This leaflet is part III of a three-part "Product Monograph" published when NTP-GLYBURIDE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NTP-GLYBURIDE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
NTP-GLYBURIDE (glyburide) is used as an adjunct to proper diet, exercise and weight reduction to lower blood glucose in adult patients with type 2 diabetes mellitus.

What it does:
NTP-GLYBURIDE lowers blood sugar by stimulating the pancreas to secrete insulin. The pancreas must produce insulin for this medication to work.

People with type 2 diabetes are not able to make enough insulin or respond normally to the insulin their bodies make. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems including kidney damage, amputations, and blindness. Diabetes is also closely linked to heart disease. The main goal of treating diabetes is to lower your blood sugar to a normal level and by doing so can prevent long term complications.

In addition to taking NTP-GLYBURIDE, you should continue to exercise and follow the diet recommended for you by your doctor.

When it should not be used:
Do not take NTP-GLYBURIDE

- If you have Type 1 diabetes.
- If you have known hypersensitivity or allergy to any sulfonylurea or sulfonamides, or to any ingredient in the formulation or component of the container.
- If you have diabetic ketoacidosis (an emergency condition with high blood glucose levels, a lack of insulin and an accumulation of ketones (chemicals) in the blood and urine). This condition should be treated with insulin.
- Diabetic precoma or coma.
- During stress conditions such as severe infections, trauma or surgery.
- In the presence of liver disease or frank jaundice; or kidney disease.
- If you are being treated with bosentan.
- If you are pregnant or breastfeeding.

What the medicinal ingredient is:
The medicinal ingredient for NTP-GLYBURIDE is glyburide.

What the important nonmedicinal ingredients are:
NTP-GLYBURIDE tablets contain the following non-medicinal ingredients: colloidal anhydrous silica, lactose monohydrate, magnesium stearate, starch (corn starch and pre-geletanized corn starch) and talc.

What dosage forms it comes in:
Tablets. Each tablet contains 2.5 mg or 5.0 mg glyburide.

WARNINGS AND PRECAUTIONS

NTP-GLYBURIDE 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 NTP-GLYBURIDE talk to your doctor or pharmacist if:

- You have or have had liver, kidney, or heart disease;
- You are pregnant or planning to get pregnant;
- You are breast-feeding.
- You have a blood disease called G6PD-deficiency anemia

NTP-GLYBURIDE 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 or high blood sugar (hypo- or hyperglycemia), especially when beginning or after changing treatment or when NTP-GLYBURIDE is not taken regularly. This may affect your ability to drive or to operate machinery.

INTERACTIONS WITH THIS MEDICATION

Ask your doctor or pharmacist before taking any other medicine, including over-the-counter products.

Drugs that can interact with NTP-GLYBURIDE include: diuretics (water pills), corticosteroids (such as prednisone), ACE inhibitors (a drug used to treat high blood pressure (hypertension)), birth control pills, and some kinds of cold and allergy drugs.

Avoid drinking alcohol while you are taking NTP-GLYBURIDE.

PROPER USE OF THIS MEDICATION

Usual dose:
Take NTP-GLYBURIDE exactly as prescribed by your doctor.

The usual dose is 2.5 to 10 mg daily. Maximum daily dose is 20 mg.

A dose of more than 10 mg should be taken in two divided doses.

Tablets should be taken during or immediately after meals.

Overdose:
Overdosage with this medication may result in ypoglycemia. If you took too many NTP-GLYBURIDE tablets at once, call your doctor or go to the emergency room of your local hospital.

Missed Dose:
If you forget to take NTP-GLYBURIDE tablets, do not take a double dose to make up for forgotten individual doses.

Discuss with your healthcare for dealing with such mistakes (in particular forgetting a dose or skipping a meal) or in the event a dose cannot be taken at the prescribed time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects:
As with any type of medication, NTP-GLYBURIDE is associated with some side effects.

The most common side effect of NTP-GLYBURIDE is low blood sugar (hypoglycemia). If your blood sugar gets too low, you may feel shaky, weak, drowsy, confused, or very hungry. You may sweat or have blurred vision, abnormal heartbeats, trouble concentrating, or a headache that doesn't go away. Signs of severe hypoglycemia can include disorientation, loss of consciousness, and seizures.

You may have low blood sugar while you are taking NTP-GLYBURIDE, especially if you miss a meal, exercise for a long time, drink alcohol or use another antidiabetic medication with NTP-GLYBURIDE. Make sure you know what to do if your blood sugar gets too low (ask your doctor, pharmacist or diabetes educator). Teach you friends, co-workers, or family members what they can do to help you if you have low blood sugar.

The following side effects have been observed with NTP-GLYBURIDE use: nausea, heartburn, feeling “full”, vomiting, diarrhea and abdominal pain.

Allergic skin reactions (itchiness, rash, eruption) have been reported in a number of patients. An increased sensibility to light has been associated with the use of oral antidiabetic drugs.

Transient visual disturbances may occur at the beginning of the treatment due to variations in level of blood sugar.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/ Effect		Talk with your doctor or pharmacist		Stop taking NTP-GLYBURIDE and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Low blood sugar (hypoglycemia)	√		
Uncommon	Skin reactions (itchiness, rash, eruption)		√	
Rare	Blood disorders (unusual bruising or bleeding)		√	
Very rare	Liver problem (yellowing of the eyes or skin)			√
	Allergic reaction (difficult breathing, decreased blood pressure)			√

This is not a complete list of side effects. For any unexpected effects while taking NTP-GLYBURIDE, contact your doctor or pharmacist.

NTP-GLYBURIDE should be stored between 15-30°C, and not beyond the expiry date indicated on the package.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor,
Teva Canada Limited.

at: 1-800-268-4127 ext. 5005
or druginfo@novopharm.com

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