# PRODUCT MONOGRAPH

**RIVA-GLYBURIDE**
**(Glyburide)**

**2.5mg and 5mg Tablets**

**Oral Hypoglycaemic**

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Control # 066015

RIVA–GLYBURIDE

(Glyburide Tablets B.P.)

2.5 mg and 5 mg

Tablets

## THERAPEUTIC CLASSIFICATION

Oral Hypoglycaemic

## ACTION AND CLINICAL PHARMACOLOGY

The main action of RIVA-GLYBURIDE (Glyburide) is to increase the release of insulin from the pancreas. Glyburide is also believed to influence other mechanisms, which cause a reduction of blood glucose.

Glyburide appears to lower the blood glucose acutely by promoting the increased secretion of insulin from the functioning beta cells of the islet tissues in the pancreas. The mechanism by which Glyburide lowers blood glucose during chronic administration has not been clearly established.

The blood glucose lowering effect of the Glyburide persists with long-term administration in non-insulin dependent diabetics, despite a gradual decline in the insulin secretory response to the drug. Extra pancreatic effects may play a part in the mechanism of action of oral sulfonylurea hypoglycaemic drugs.

In addition to its blood glucose lowering effect, Glyburide enhances renal free water clearance producing a mild diuresis. Clinical experience to date indicates an extremely low incidence of disulfiram-like reactions in patients while taking Glyburide.

Glyburide as a micronized powder is well absorbed from the intestinal tract and after absorption, Glyburide is highly bound to plasma proteins. In the liver, it is completely metabolised to the 3–cis and 4–trans derivatives by hydroxylation of the cyclohexyl ring and the kidneys play only a minor role in their biotransformation and elimination from plasma. Essentially no hypoglycaemic effect is produced by the metabolites and they are not stored in the body but are eliminated through the bile and in approximately equal amounts in the urine (conjugated to glucuronic acid) and in the faeces. This is qualitatively different from that of other sulfonylureas, which are excreted primarily in the urine.

In normal subjects, maximal plasma levels of insulin were reached in 90 minutes following a 5 mg oral dose of Glyburide.

After a 5 mg oral dose of Glyburide, blood glucose levels reached a minimum after 90 to 120 minutes in normal subjects corresponding to a 54% mean reduction.

It has been reported that Glyburide had a much more persistent effect on insulin secretion than tolbutamide, stimulating insulin secretion as long as two months after initiation of therapy. Reports have estimated the effectiveness of Glyburide as 100 to 200 times that of tolbutamide. On a weight basis, a daily dose of 5 mg Glyburide controlled blood glucose concentrations to approximately the same degree as a daily dose of 1 to 1.5 g tolbutamide.

A comparative two–way, single–dose bioavailability study was performed on RIVA-GLYBURIDE (Glyburide) 5 mg Tablets and DIABETA® (Glyburide) 5 mg Tablets. The pharmacokinetic data calculated for the RIVA-GLYBURIDE and DIABETA® tablet formulations is tabulated below:

| | RIVA-GLYBURIDE (2 x 5 mg Tablets) | DIABETA® (2 x 5 mg Tablets) | Percentage of DIABETA® |
|---|---|---|---|
| $AUC_T$* (ng• h/mL) | 1339.43 (34) | 1286.91 (32) | 104% |
| $AUC_I$* (ng• h/mL) | 1408.10 (33) | 1339.43 (33) | 105% |
| $C_{max}$* (ng/mL) | 242.26 (31) | 249.64 (22) | 97% |
| $T_{max}$+ (h) | 4.09 (1) | 4.00 (1) | — |
| $T_{1/2}$ +(h) | 3.13 (1) | 2.99 (2) | — |

(*) Geometric means (CV)

(+) Arithmetic means (SD)

## INDICATIONS AND CLINICAL USE

RIVA-GLYBURIDE (Glyburide) is indicated for the control of hyperglycaemia in Glyburide–responsive diabetes mellitus of stable, mild, non ketosis–prone, maturity–onset or adult type which cannot be controlled by the proper management of diet and exercise, or when therapy with insulin is inappropriate.

## CONTRAINDICATIONS

Patients who are known to be hypersensitive or allergic to Glyburide should not be given RIVA-GLYBURIDE (Glyburide). Patients with unstable and/or insulin–dependent diabetes mellitus; ketoacidosis; coma; stress conditions such as severe infections, trauma or surgery;

liver disease or renal impairment; or with frank jaundice should not be given Glyburide. Oral antidiabetic drugs should not be given during pregnancy. RIVA-GLYBURIDE is also contraindicated for patients with pre–existing complications peculiar to diabetes.

## WARNINGS

Using RIVA-GLYBURIDE (Glyburide) may not prevent the development of complications peculiar to diabetes mellitus.

RIVA-GLYBURIDE must not be considered as a substitute for diet but must be used as treatment in addition to a proper dietary regime.

With time, a patient's diabetic state deteriorates and the patient may become progressively less responsive to oral hypoglycaemic therapy. Glyburide should be withdrawn if blood glucose is not adequately lowered in response to the drug.

## PRECAUTIONS

Patient Selection and Follow–Up:

It is important to carefully select patients. Strict attention to diet, careful adjustment of dosage, instruction of the patient on hypoglycaemic reactions and their control and complete follow–up examinations are imperative.

Patients receiving oral hypoglycaemics must be carefully monitored for short– and long–term complications as it is not fully understood what the effects of these agents are on the vascular changes and other long–term sequelae of diabetes mellitus.

It is advisable that cardiovascular, ophthalmic, haematological, renal and hepatic status be assessed periodically.

In patients with Addison's disease, oral hypoglycaemics should be administered cautiously.

Loss of Control of Blood Glucose:

When a patient, stabilised on any diabetic regimen, is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue RIVA-GLYBURIDE (Glyburide) and administer insulin.

The effectiveness of any oral hypoglycaemic drug, including RIVA-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 is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given.

Laboratory Tests:

Blood and urine glucose should be monitored periodically. Measurement of glycosylated haemoglobin may be useful.

Use in Pregnancy:

Teratogenic Effects: Reproduction studies, with rats and rabbits given Glyburide doses up to 500 times the human dose, have revealed no evidence of impaired fertility or harm to the foetus. However, no adequate and well–controlled studies have been done with pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly indicated.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycaemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half lives. If Glyburide is used during pregnancy, it should be discontinued at least two weeks before the expected delivery date.

Use in Nursing Mothers:

Although it is not known whether Glyburide is excreted in human milk, some sulfonylureas are known to be excreted in human milk. Because the potential for hypoglycaemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue drug administration, taking into account the importance of the drug to the mother. If RIVA-GLYBURIDE is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Paediatric Use:

Safety and effectiveness in children have not been established.

Hypoglycaemic Reactions:

All sulfonylurea drugs can induce severe hypoglycaemia. Elderly patients, patients with impaired hepatic or renal function, debilitated or malnourished patients and patients with primary or secondary adrenal insufficiency are particularly sensitive. Hypoglycaemia may be

difficult to recognise in the elderly, and in patients who are taking ß–adrenergic blocking drugs. Hypoglycaemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose–lowering drug is use.

Drug Interactions:

When agents such as sulphonamides, tuberculostatics, phenylbutazone, clofibrate, monoamine oxidase inhibitors, coumarin derivatives, salicylates, chloramphenicol, nonsteroidal anti–inflammatory agents, probenecid, ß–adrenergic blocking agents, and other drugs that are highly protein bound are used concurrently with sulfonylureas, hypoglycaemia may be potentiated due to drug interactions. When such drugs are administered to a patient receiving Glyburide, the patient should be observed for hypoglycaemia. When such drugs are withdrawn from a patient receiving Glyburide, the patient should be observed for loss of blood sugar control.

Pharmacological doses of diuretics (thiazides, furosemide), corticosteroids, estrogens, oral contraceptives (oestrogen plus progestogen), phenothiazines, thyroid products, phenytoin, sympathomimetics, calcium channel blocking drugs, isoniazid and nicotinic acid tend to cause hyperglycaemia and may lead to a loss of control of blood sugar.

When such drugs are administered to a patient receiving Glyburide, the patient should be observed for loss of blood sugar control. When such drugs are withdrawn from a patient receiving Glyburide the patient should be observed for hypoglycaemia.

In patients taking an oral hypoglycaemic agent, barbiturates should be administered with caution since barbiturate action may be prolonged.

Treatment with oral sulfonylurea agents may cause alcohol intolerance (disulfiram–like reaction: flushing, sensation of warmth, giddiness, nausea and sometimes tachycardia). Avoidance of alcohol will prevent the occurrence of this reaction.

A potential interaction between oral miconazole and oral hypoglycaemic agents leading to severe hypoglycaemia has been reported; whether this interaction also occurs with intravenous, topical or vaginal preparations of miconazole is not known.

## ADVERSE REACTIONS

Hypoglycaemia: (See PRECAUTIONS)

The most severe adverse reaction to Glyburide is hypoglycaemia, which has occasionally been fatal. Severe hypoglycaemia may mimic acute CNS disorders. Suggestive signs or symptoms of hypoglycaemia may include: dizziness, headache, nervousness, weakness, sweating, visual impairment, tremor, pallor, mental confusion, parenthesis, diplopia, insomnia, fatigue, anxiety, somnolence, lethargy and coma. The predisposing factors may include hepatic and/or renal disease, malnutrition, debility, advanced age, alcoholism or adrenal or pituitary insufficiency.

Gastrointestinal Reactions:

Adverse gastrointestinal effects such as nausea, epigastric fullness and heartburn are the most common adverse reactions to Glyburide, occurring in about 1 to 2% of patients. Since these reactions tend to be related to the dose, they may be discontinued by a reduction in dosage. Rarely, during therapy with oral hypoglycaemic agents, there have been reports of jaundice.

Adverse reactions, grouped by system, are as follows:

Dermatological Reactions:

In a small number of patients, there have been reports of allergic skin reactions such as pruritus, erythema, urticaria or morbilliform or maculopapular eruptions. These may subside on continued use of RIVA-GLYBURIDE (Glyburide); however, the drug should be discontinued if they persist. Therapy with oral hypoglycaemic agents has been associated with porphyria cutanea tarda and photosensitivity reactions.

Haematological Reactions:

There have been reports of leukopenia, agranulocytosis, thrombocytopenia, haemolytic anaemia and aplastic anaemia.

Metabolic Reactions:

In patients undergoing treatment with oral hypoglycaemic agents, hepatic prophyria and disulfiram–like reactions have been noted.

Endocrine Reactions:

In patients treated with oral hypoglycaemic drugs, a reduction in the uptake of iodine by the thyroid gland has been noted.

Clinical Laboratory:

There have been reports of elevated creatinine, elevated SGOT, elevated alkaline phosphatase, elevated uric acid, elevated WBC, decreased WBC, decreased haemoglobin, elevated bilirubin and neutropenia.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

Hypoglycaemia may be the outcome of overdosage with sulfonylureas; however, there is a wide variation in the dosage which results in hypoglycaemia and the dosage in sensitive patients may be within the accepted therapeutic range.

In mild cases, hypoglycaemia manifests itself as sweating, flushing or pallor, numbness, chilliness, hunger, trembling, headache, dizziness, increased pulse rate, palpitations, increase in blood pressure and apprehensiveness. Coma appears in more severe cases. However, the symptoms of hypoglycaemia are not necessarily as typical as described above and symptoms of cerebrovascular insufficiency may be mimicked by sulfonylureas.

The medication should be discontinued and hypoglycaemia should be treated with the prompt administration of a sufficient quantity of dextrose.

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

## DOSAGE AND ADMINISTRATION

The management of blood glucose levels has no fixed dosage regimen in subjects with diabetes. The minimum dose that will adequately lower the blood glucose should be determined individually.

Initially, if the blood glucose is not adequately reduced in patients by the maximal recommended dose, RIVA-GLYBURIDE (Glyburide) should be withdrawn. A loss of effectiveness may occur during the course of therapy. Discontinuation of the drug while closely observing the patient is advisable once or twice a year in order to determine the effectiveness of the drug in controlling the blood glucose. The drug should not be resumed if there is no evidence that it is necessary. During periods of a transient loss in the control of blood sugar, administration of the drug for a short term may be adequate in some subjects with diabetes.

Newly–Diagnosed Diabetics:

Initially, 5 mg (2.5 mg in patients over 60 years of age) should be administered daily for 5 to 7 days. Dosage should then be increased or decreased by aliquots of 2.5 mg depending on the response up to a maximum daily dose of 20 mg (because there is normally no additional effect on control of the metabolic state at higher doses). Sometimes, 2.5 mg daily maintains control but the majority of cases are controlled by a single dose of 5 mg to 10 mg (1 to 2 tablets) daily administered during or immediately following breakfast. The first daily dose should be postponed until lunchtime in patients who eat only a light breakfast. In patients who require more than 10 mg (2 tablets) daily, the excess should be administered with the evening meal.

Changeover from Other Hypoglycaemic Agents:

Previous oral medication should be withdrawn and RIVA-GLYBURIDE 5 mg daily (2.5 mg in patients over 60 years of age) should be initiated. Maintenance should be determined as in newly–diagnosed diabetics.

Changeover from Insulin:

If in a patient with stable, mild, maturity–onset diabetes a change from insulin to RIVA-GLYBURIDE is considered, insulin treatment should be withdrawn for two or three days to ascertain whether or not therapy, other than regulation of diet and exercise, is necessary. The patient's urine should be tested for glucose and ketone bodies at least three times daily during this insulin–free period and the results should be closely monitored by the physician. The appearance of significant ketonuria together with glycosuria within 12 to 24 hours after the discontinuation of insulin provides strong evidence that the patient is ketosis–prone, and precludes the change from insulin to Glyburide.

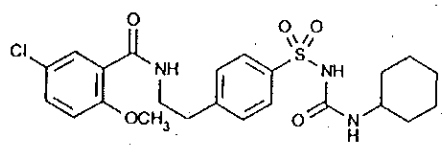
## PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: Glyburide B.P.

Chemical Name: N4–[2–(5–chloro–2–methoxybenzamido)–ethyl]–phenyl–sulphonyl–N'–cyclohexylurea.

Structural Formula:



Molecular Formula: $C_{23}H_{28}ClN_3O_5S$ Molecular Weight: 494

Description: Glyburide is white, crystalline, tasteless, odourless powder which is readily soluble in dimethylformamide, sparingly soluble with salt formation in alkali, very sparingly soluble in ethanol and chloroform and practically insoluble in water and dilute acids. It has a melting range of 172° – 174°C and pKa of 5.3.

## AVAILABILITY OF DOSAGE FORMS

RIVA-GLYBURIDE is available as white round tablets containing 2.5 mg of Glyburide with broken scoreline and stylised "R" engraved on one side and "2.5" on the other side. Available in bottles of 100 and 500 tablets, and in boxes of 30 and 100 as unit dose strips.

RIVA-GLYBURIDE is also available as white capsule–shaped tablets containing 5 mg of Glyburide with stylised "R", scoreline and "5" engraved on one side and plain on the other side. Available in bottles of 100 and 500 tablets, and in boxes of 30 and 100 as unit dose strips.

## STABILITY AND STORAGE RECOMMENDATIONS

Store between 15–30°C.

Unit dose strips should be stored between 15– 25°C and protected from high humidity.

## PHARMACOLOGY

Glyburide caused a rise in insulin output in the isolated rat pancreas. Insulin was promptly and significantly released from isolated rat pancreatic islets in the presence of 0.6 µg/mL of Glyburide.

It has been reported that insulin secretion stimulated by sulfonylurea is inhibited by propranolol, a beta–adrenergic blocker, in the dog and that the Glyburide–induced hypoglycaemia in the presence of propranolol could be the result of extra–pancreatic effects.

In single–dose studies with normal subjects, Glyburide demonstrated significant absorption within one hour, peak drug levels at about four hours, and low but detectable levels at twenty–four hours. As reflected by areas under the serum concentration–time curve, the mean serum levels of Glyburide increased in proportion to a corresponding increase in dose. With multiple dose studies of diabetic patients, Glyburide demonstrated 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 fasting normal subjects, single–dose studies showed that 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. In non–fasting diabetic patients, the blood glucose lowering effect persisted for 24 hours after single morning doses. However, there is no reliable correlation between blood drug levels and fasting blood glucose levels when Glyburide is administered repeatedly in diabetic patients. A one–year study of diabetic patients treated with Glyburide showed no reliable correlation between administered dose and serum drug level.

It has been found that the half–lives of some sulfonylureas were prolonged by certain sulphonamides. This resulted in higher insulin and serum concentrations of Glyburide; therefore, hypoglycaemic attacks could be expected.

Hypoglycaemia has been observed with the addition of phenylbutazone to Glyburide and it has been confirmed that the Glyburide–induced reduction in blood sugar is enhanced by phenylbutazone, which resulted in higher insulin levels. Administration of phenylbutazone had no effect on the metabolism of Glyburide. However, it was found that the renal excretion of the main metabolite of Glyburide was significantly reduced.

*In vitro*, the protein binding of Glyburide is predominantly non–ionic, whereas that of other sulfonylureas (chloropropamide, tolbutamide, tolazamide) is ionic. Acidic drugs like phenylbutazone, warfarin, and salicylates displace the ionic–binding sulfonylureas from serum proteins to a far greater extent than the non–ionic binding Glyburide. However, it has not been shown in clinical use that this difference in protein binding will result in fewer drug–drug interactions with Glyburide.

## TOXICOLOGY

Acute Toxicity:

| Species | Route of Administration | LD50 (mg/kg) |
|---|---|---|
| Rat | (1) p.o. | >3200 |
| | (2) p.o. | >15000 |
| | i.p. | >3200 |
| Mouse | i.p. | >2000 |
| Rabbit | p.o. | >10000 |
| Dog | p.o. | >10000 |

Chronic Toxicity:

Rats:

Two 18–month studies were performed in rats. Each group was made up of 15 males and 15 females. Doses of 0.11, 1.0 and 11 mg/kg Glyburide were administered in the diet in one of the studies. After 3 months, no drug–induced toxic effects were observed and hypoglycaemia was not present.

In the other study, doses of 30, 100 and 300 mg/kg Glyburide were administered in the diet. Petechiae in the thymus, fatty metamorphosis in the corpora lutea and thrombosis in the myometrial artery were observed in the mid and high dose groups. High dose rats had loose connective tissue in the ovaries, decreased glucose tolerance, reduced pancreatic ß–cell granulation and increased kidney and adrenal weights. There was no evidence of carcinogenesis.

Dogs:

Dogs (3 males and 3 females/group) received doses of 0.2, 2 and 20 mg/kg Glyburide in their diet in an 18–month study. The high–dose dogs exhibited gastrointestinal irritation, decreased glucose tolerance and reduced ß–cell granulation.

In a 12–month study in dogs receiving 3, 100 and 300 mg/kg Glyburide in capsules, a small atrophic thymus was observed at all 3 dosage levels. No other abnormalities were found.

Rabbits:

Glyburide was administered to rabbits (5 to 8 males and females/group) at doses of 1.6 to 1.9, 9 and 42 mg/kg in the diet in a 6–month study. Hypoglycaemia was scattered among all 3 of the dosage levels. At the mid and high doses, there was a slight increase in BUN and at the high dose, serum proteins were decreased.

A 12–month study was also performed in which doses of 30, 100 and 300 mg/kg Glyburide were administered in the diet. There were 7 to 9 male and female rabbits/group. Hypoglycaemia was again scattered among all of the dosage levels. At termination, treated animals demonstrated higher blood glucose and cholesterol levels than did controls.

Reproduction and Teratology:

At oral doses of 0.2, 20 and 2000 mg/kg Glyburide, there was no evidence of teratogenic effects in the rat or the mouse; although at the high dose in the rat, there was some delay in the embryonic growth. Similarly, malformations attributed to the drug were not produced by oral doses of 100 and 300 mg/kg Glyburide in the Dutch Belted rabbit. Hypoglycaemia was probably the cause of increased resorptions and reductions of live births.

There was no dose related effect on the male or female reproductive activities in the rat with oral doses of 100 and 300 mg/kg/day Glyburide. Continuous administration of the drug through gestation, parturition and lactation did not inflict damaging effects on the dams or the pups at birth or at weaning.

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