If necessary, adjust the dosage of the anti-diabetic agent during treatment with the neuroleptic and after it has been discontinued.

Glucocorticoids (systemic and local route: intra-articular, cutaneous and rectal preparations) and tetracosactrin
Increase in blood glucose levels with possible ketosis (reduced tolerance to carbohydrates due to glucocorticoids).
Beta-2 sympathomimetics (ritodrine, salbutamol, terbutaline)
Increased blood glucose levels by beta2-stimulants. Emphasise the need for monitoring of blood glucose levels. If necessary, switch to insulin treatment.

Pregnancy & Lactation
Pregnancy:
There is no data concerning the use of Gliclazide in pregnant woman; there are few data with other sulfonylurea. Control of diabetes should be obtained before the time of conception to reduce the risk of congenital abnormalities due to uncontrolled diabetes. During pregnancy, oral antidiabetic agents are not suitable, so insulin is the first choice for the treatment of diabetes. It is recommended that oral hypoglycaemic therapy is changed to insulin before a pregnancy is attempted, or as soon as pregnancy is discovered.

Breast-feeding:
It is not known whether Gliclazide or its metabolites are excreted in breast milk. Given the risk of neonatal hypoglycaemia, gliclazide is contra-indicated in breast-feeding mother.

Side Effects:
Hypoglycaemia
As for other sulphonylureas, treatment with gliclazide tablets can cause hypoglycaemia, if mealtimes are irregular and, in particular, if meals are skipped. Possible symptoms of hypoglycaemia are: headache, intense hunger, nausea, vomiting, lassitude, sleep disorders, agitation, aggression, poor concentration, reduced awareness and slowed reactions, depression, confusion, visual and speech disorders, aphasia, tremor, paresis, sensory disorders, dizziness, 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: sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmia. Usually, 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.
Gastrointestinal disturbances, including abdominal pain, nausea, vomiting dyspepsia, diarrhoea, and constipation have been reported: if these should occur they can be avoided or minimised if gliclazide is taken with breakfast.

The following undesirable effects have been more rarely reported:
Skin and subcutaneous tissue disorders
Rash, pruritus, urticaria, erythema, maculopapular rashes, bullous reactions.

Blood and lymphatic system disorders
Changes in haematology are rare. They may include anaemia, leucopenia, thrombocytopenia, granulocytopenia. These are in general reversible upon discontinuation of medication.

Hepato-biliary disorders
Raised hepatic enzyme levels (AST, ALT, alkaline phosphatase), hepatitis (isolated reports). Discontinue treatment if cholestatic jaundice appears. These symptoms usually disappear after discontinuation of treatment.

Eye disorders
Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.

Class attribution effects
Cases of erythrocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia and allergic vasculitis, have been described for other sulphonylureas. With other sulphonylureas cases were also observed of elevated liver enzyme levels and even impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis which regressed after withdrawal of the sulphonylurea or led to life-threatening liver failure in isolated cases.

Symptoms & Treatment of Overdose :
An overdose of sulphonylureas may lead to hypoglycaemia. Moderate symptoms of hypoglycaemia, with no loss of consciousness or neurological signs, should be completely corrected by the administration of carbohydrates and by adjusting the dosage and/or dietary measures. The patient should be closely monitored until the doctor is sure that he/she is out of danger.

Severe hypoglycaemic reactions, with coma, convulsions or other neurological disorders, are possible and constitute a medical emergency requiring the immediate hospitalisation of the patient.

If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of 50ml of a concentrated glucose solution (20% to 30%), followed by a continuous infusion of a more dilute glucose solution (10 %) at a rate necessary to maintain blood glucose levels above 1g/L.

Plasma clearance of gliclazide may be prolonged in patients suffering from a hepatic disorder. Dialysis is of no value as gliclazide is highly protein-bound

Storage:
Store in a dry place (below 30°C). Protect from light.

Shelf Life:
2 years

Pack Size:
Blister pack of 6x10's, 10x10's, 12x10's and 50x10's.

Products Registration Number:
MAL

Further information can be obtained from your doctor or pharmacist.

ROYCE®

Product Holder/Manufactured by:
ROYCE PHARMA MFG.SDN.BHD. (650435-X)
PT 1663, Nilai Industrial Estate,
71800 Nilai, Negeri Sembilan,
Malaysia.

RPI 099-01
0906 16

ROYCE®

Rolazide Tablet 80mg

Presentation:
White to off white, round shaped tablet with cross break line on one side and blank on the other side.

Content:
Each tablet contains:
Gliclazide 80mg

Phamacological Information:
Gliclazide is a hypoglycaemic sulphonylurea antidiabetic active substance differing from other related compounds by an N-containing heterocyclic ring with an endocyclic bond. Gliclazide reduces blood glucose levels by stimulating the secretion of insulin by the beta cells of the islets of Langerhans. In type 2 diabetics, gliclazide restores early peak insulin secretion in the presence of glucose, and increases the second phase of insulin secretion. A significant increase in insulin response is observed following a meal or a glucose stimulus. In addition to these metabolic properties, gliclazide has haemovascular properties. Gliclazide reduces the process of microthrombosis by two mechanisms which may be involved in the complications of diabetes :
-partial inhibition of platelet adhesiveness and aggregation with a reduction in the markers of platelet activation (beta-thromboglobulin, thromboxane B2),
-an effect on the fibrinolytic activity of the vascular endothelium (increase in tPA activity).

Gliclazide is rapidly absorbed from the gastrointestinal tract and maximum blood concentrations are attained between the 11th and the 14th hour. Protein binding is 94.2 % in humans. Since the apparent half-life of final elimination of gliclazide is twenty hours in humans, the treatment may be administered as two daily doses. Elimination takes place mainly in urine: less than 1 % of the ingested dose is found unchanged in urine.

Indications:
Non-insulin-dependent diabetes (type 2), in adults, when dietary measures, physical exercise and weight loss alone are not sufficient to control blood glucose levels.

Dosage and Administration:
For oral use only.

For adults only. As with all hypoglycaemic agents, the dosage must be adapted to suit each individual case. In the case of a transient disturbance of glucose control, administration of the product for a

short period of time may be sufficient in a patient in whom the glucose balance is normally well maintained by dietary measures.

Subjects under the age of 65 years
Initial dose - The recommended initial dose is 1 tablet per day.
Dosage increments - The dosage is usually adjusted in increments of 1 tablet depending on the glycaemic response. Each dosage increment should be separated by at least 14 days.
Maintenance treatment - The dosage varies from 1 to 3 tablets per day, 4 in exceptional cases.
The standard dosage is 2 tablets per day, taken as 2 daily doses.

Subjects over the age of 65 years.
Begin the treatment with ½ tablet taken once a day. This dosage may be progressively increased until satisfactory glucose control is obtained in the patient, provided that an interval of at least 14 days is maintained after each dosage increase and blood sugar levels are monitored closely.

High-risk patients
In patients who are undernourished or with a marked change in their general state or whose calorie intake is irregular, and in patients with renal or hepatic insufficiency, treatment must be initiated at the lowest dose and the guidelines for dosage increases scrupulously respected, so as to avoid any hypoglycaemic reactions

Patients receiving other oral hypoglycaemic agents
As with all hypoglycaemic sulphonylureas, this drug may replace other anti-diabetic treatments without any transition period. On changing from a hypoglycaemic sulphonylurea with a longer half-life (e.g. chlorpropamide) to this drug, patients should be closely monitored (over several weeks) to avoid the occurrence of hypoglycaemia, due to the possibility of an overlap of the therapeutic effects.

Contraindication:
The use of this medicine is contra-indicated in the following cases :
- hypersensitivity to gliclazide or other sulphonylureas or sulphonamides, or to any of the excipients used,
- insulin-dependent diabetes, particularly juvenile diabetes, diabetes complicated by ketosis and acidosis, or diabetic precoma,
- severe hepatic or renal insufficiency,
- treatment with miconazole
- breast-feeding

In general, it is not advisable to combine this drug with phenylbutazone, danazol or alcohol.

Warning & Precaution:
Hypoglycaemia
Hypoglycaemia may occur during treatment with hypoglycaemic sulphonylureas. Some cases may be severe and prolonged. Hospitalisation may be required and blood sugar levels should be corrected for several days if necessary. Careful selection of the patient and the dosage, as well as keeping the patient adequately informed are necessary to avoid episodes of hypoglycaemia.
Patients who are elderly, undernourished or with a change in their general state, and patients with adrenal insufficiency or hypopituitarism are particularly sensitive to the hypoglycaemic effects of anti-diabetic agents. Hypoglycaemia may be difficult to diagnose in elderly subjects and patients treated with beta-blockers.
This treatment should only be prescribed if the patient is likely to eat regularly (including breakfast). A regular intake of carbohydrates is important due to the increased risk of hypoglycaemia if meals are taken late, in cases of inadequate diet or if the diet contains an inadequate balance of carbohydrates. Hypoglycaemia is more likely to occur in subjects following a low-calorie diet, after considerable or prolonged exertion, after the consumption of alcohol or during the administration of a combination of hypoglycaemic agents.
Renal or hepatic insufficiency may alter the distribution of gliclazide and hepatic insufficiency may also reduce the capacity for gluconeogenesis; these two effects increase the risk of serious hypoglycaemic reactions.

Glycaemic imbalance
Control of blood glucose levels by anti-diabetic agents may be reduced in patients with fever, trauma or infection or in patients undergoing surgery. In these cases, it may be necessary to discontinue the treatment and administer insulin.
The efficacy of all oral hypoglycaemic agents, including gliclazide, in lowering blood sugar to the desired level decreases in the long term in many patients. This may be due to an increase in the severity of the diabetes or to a reduced response to the treatment. This phenomenon is known as secondary failure and should be distinguished from primary failure, in which the drug proves to be ineffective when prescribed as first-line treatment for a given patient. Adequate dosage adjustment and observation of the diet must be considered before classing the patient as a secondary failure.

Biological tests
Blood and urinary glucose levels should be monitored periodically. Measurements of glycosylated haemoglobin levels may prove to be useful.

Renal and hepatic insufficiency
The pharmacokinetics and/or pharmacodynamics of gliclazide may be altered in patients with renal or hepatic insufficiency. If hypoglycaemia occurs in these patients and there is a risk that it will be prolonged, an appropriate treatment should be instituted.

Carriers of a G6PD (glucose-6-phosphate dehydrogenase) enzyme deficiency
Medicinal products of the sulphonylurea class can cause a haemolytic anaemia in patients who are carriers of a G6PD enzyme deficiency. As gliclazide belongs to this class, precautions must be taken in G6PD deficient patients and a treatment from another therapeutic class other than sulphonylureas must be envisaged.

Patient information
The risks of hypoglycaemia, together with its symptoms, treatment, and conditions that predispose to its development, should be explained to the patient and to family members. The patient should be informed of the importance of following dietary advice, of taking regular exercise, and of regular monitoring of blood glucose levels.

Effects on ability to drive and use machines
Patients should be made aware of the symptoms of hypoglycaemia and should be careful when driving and/or operating machinery, especially at the beginning of treatment.

Drug Interaction:
1) The following products are likely to increase hypoglycaemia
Contra-indicated association

Miconazole (systemic route, oral gel)
Increase in the hypoglycaemic effect with possible occurrence of hypoglycaemic symptoms, or even coma.

Inadvisable associations

Phenylbutazone (systemic route)
Increase in the hypoglycaemic effect of sulphonylureas (displacement of plasma protein binding and/or decrease in their elimination). An alternative anti-inflammatory agent with less potential for interaction should preferably be used, otherwise to warn the patient and emphasize the need for self-monitoring; if necessary, adjust the dosage of gliclazide during treatment with the anti-inflammatory agent and after it has been discontinued.

Alcohol
Increased hypoglycaemic reaction (inhibition of compensatory mechanisms), which may increase the likelihood of hypoglycaemic coma. Avoid the consumption of alcoholic drinks and medicines containing alcohol.

Combinations requiring precautions

Beta-blockers
All beta-blockers mask certain symptoms of hypoglycaemia : palpitations and tachycardia. Most non-cardioselective beta-blockers increase the incidence and severity of hypoglycaemia. Inform the patient and encourage self-monitoring of blood glucose levels, particularly at the start of treatment.

Fluconazole
Increase in the half-life of the sulphonylurea with the possible occurrence of hypoglycaemic symptoms. Inform the patient, emphasise the need for self-monitoring of blood glucose levels and, if necessary, adjust the dosage of the sulphonylurea during treatment with fluconazole.

Inhibitors of angiotensin converting enzyme (described for captopril, enalapril)
The use of angiotensin converting enzyme inhibitors may lead to an increase in the hypoglycaemic effect in diabetic patients treated with hypoglycaemic sulphonylureas. Symptoms of hypoglycaemia appear to be an exceptional occurrence. One theory put forward is that an improvement in glucose tolerance results in a reduction in insulin requirements. Emphasise the need for self-monitoring of blood glucose levels.

2) Products which may cause an increase in blood sugar levels
Inadvisable association

Danazol (diabetogenic effect of Danazol)
If the combination is unavoidable, warn the patient of the potential risk and emphasise the need for self-monitoring of blood and urinary glucose levels. If necessary, adjust the dosage of the anti-diabetic agent during treatment with Danazol and after it has been discontinued.

Combinations requiring special precautions

Chlorpromazine (neuroleptics)
At high doses (100 mg per day of chlorpromazine) blood sugar levels may be raised (decrease in the release of insulin). Inform the patient and emphasise the need for self-monitoring of blood glucose levels.