**IDAMAN PHARMA MANUFACTURING**

**IDAMAN PHARMA GLICLAZIDE TABLET 80MG**

**DESCRIPTION**
White to off white, round, flat, bevelled- edge tablet and scored on one side.
**Each tablet contains:** Gliclazide 80mg

**ROUTE OF ADMINISTRATION**
Oral

**PHARMACODYNAMICS**
Pharmacotherapeutic group: sulphonamides, urea derivatives. ATC code: A10BB09

***Mechanism of action***
Gliclazide is a hypoglycaemic sulfonylurea 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 insulin secretion from the β-cells of the islets of Langerhans. Increase in postprandial insulin and C-peptide secretion persists aftertwo years of treatment. In addition to these metabolic properties, gliclazide has haemovascular properties.

***Effects on insulin release***
In type 2 diabetics, gliclazide restores the first peak of insulin secretion in response to glucose and increases the second phase of insulin secretion. A significant increase in insulin response is seen in response to stimulation induced by a meal or glucose.

***Haemovascular properties***
Gliclazide decreases microthrombosis by two mechanisms which may be involved in complications of diabetes:
• A partial inhibition of platelet aggregation and adhesion, with a decrease in the markers of platelet activation (beta thromboglobulin, thromboxane B2),
• An action on the vascular endothelium fibrinolytic activity with an increase in tPA activity.

**PHARMACOKINETICS**
***Absorption***
Plasma levels increase reaching maximal concentrationsbetween 2 and 6 hours. Gliclazide is well absorbed. Food intake does not affect the rate or degree of absorption.

***Distribution***
Plasma protein binding is approximately 95%. The volume of distribution is around 19 liters.

***Biotransformation***
Gliclazide is mainly metabolised in the liver and excreted in the urine; less than 1% of the dose is excreted unchanged in the urine. No active metabolites have been detected in plasma.

***Elimination***
The elimination half-life of gliclazide is between 10 and 12 hours.

***Linearity/non-linearity***
The relationship between the dose administered between 40 and 400mg and the mean plasma concentrations is linear.

***Special populations***
Elderly. No clinically significant changes in pharmacokinetic parameters have been observed in elderly patients

**INDICATION**
Non-insulin dependent diabetes, in association with an adapted diet, in cases where dietary measures alone provide inadequate control blood glucose levels.

**RECOMMENDED DOSAGE**
*RESTRICTED TO ADULTS.*
As with any hypoglycemic agent, the dosages should beadjusted to the particular circumstances. In the event of a transitory loss of blood glucose control in a patient where good control is usually achieved by diet, it may be sufficient to administer this product for a short period.

***Patients under the age of 65***
Initial dose:
The recommended initial dose is one tablet per day.
Dosage steps:
Adjustments in posology are usually made in steps of one tablet at a time, depending on the response in blood glucose. At least 14 days should separate successive steps in the dose.
Maintenance treatment:
The posology can vary from 1 to 3, or rarely 4, tablets per day.
The standard dosage is 2 tablets a day, as 2 daily doses.

Patients at particular risk:-
***Patients over the age of 65:***
Begin the treatment with a half-tablet once a day.
The dose can be progressively increased until the patient's blood glucose is satisfactorily controlled, while keeping to steps of at least 14 days between successive levels, and with close monitoring of blood glucose.

Other patients at particular risk:-
In patients who are malnourished or showing markedly poor general state of health, or whose calorie intake is irregular, or whose kidney or liver function is impaired, treatment should be begun at the lowest dose. The stepwise increases in dosagemust be scrupulously adhered to in order to avoid a hypoglycemic reaction.

***Patients treated with other oral hypoglycaemic agents:***
As with any sulfonylurea, this medicinal product can be used as follow-on from another antidiabetic drug, without any transitional period being needed. When patients change to this medication from a sulfonylurea with a longer half-life (such as chlorpropamide), they must be closely monitored (for several weeks). This is to avoid the possible occurrence of hypoglycaemia due to an overlapping of effects from the two treatments.

***Paediatric population:***
The safety and efficacy of gliclazide 80mg in children and adolescents have not been established. No data are available.

**CONTRAINDICATIONS**

This medicine is contra-indicated in case of:

- Hypersensitivity to gliclazide or to any of the excipients in the formulation, other sulfonylureas, sulfonamides
- Type 1 diabetes
- Diabetic pre-coma and coma, diabetic keto-acidosis
- Severe renal or hepatic insufficiency; in these cases the use of insulin is recommended
- Treatment with miconazole
- Lactation
- Gliclazide should, where possible, be avoided in porphyria.

**WARNING AND PRECAUTIONS**

***Hypoglycaemia:-***

This treatment should be prescribed only if the patient is likely to have a regular food intake (including breakfast). It is important to have a regular carbohydrate intake due to theincreased risk of hypoglycaemia if a meal is taken late, if an inadequate amount of food is consumed or if the food is low in carbohydrate. Hypoglycaemia is more likely to occur during low-calorie diets, following prolonged or strenuous exercise, alcohol intake or if a combination of hypoglycaemic agents is being used.

Hypoglycaemia may occur following administration of sulfonylureas. Some cases may be severe and prolonged. Hospitalisation may be necessary and glucose administrationmay need to be continued for several days.

Careful selection of patients, of the dose used, and clear patient directions are necessary to reduce the risk of hypoglycaemic episodes.

Factors which increase the risk of hypoglycaemia:

- Patient refuses or (particularly in elderly subjects) is unable to co-operate
- Malnutrition, irregular mealtimes, skipping meals, periods of fasting or dietary change
- Imbalance between physical exercise and carbohydrate intake
- Renal insufficiency
- Overdose of Gliclazide 80mg tablets
- Severe hepatic insufficiency
- Certain endocrine disorders: thyroid disorders, hypopituitarism, and adrenal insufficiency
- Concomitant administration of certain other medicines

Renal and hepatic insufficiency: the pharmacokinetics and/or pharmacodynamics of gliclazide may be altered in patients with hepatic insufficiency or severe renal failure. A hypoglycaemic episode occurring in these patients may be prolonged, so appropriate management should be initiated.

Patient information: the risks of hypoglycaemia, together withits 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.

Poor blood glucose control: blood glucose control in a patient receiving antidiabetic treatment may be affected by any of the following: fever, trauma, infection or surgical intervention. In some cases, it may be necessary to administer insulin.

The hypoglycaemic efficacy of any oral antidiabetic agent, including gliclazide, is attenuated over time in many patients: this may be due to progression in the severity of the diabetes,or to a reduced response to treatment. This phenomenon is known as secondary failure which is distinct from primary failure, when an active substance is ineffective as first-line treatment. Adequate dose adjustment and dietary compliance should be considered before classifying the patient as secondary failure.

***Dysglycaemia:-***

Disturbances in blood glucose, including hypoglycaemia and hyperglycemia have been reported, in diabetic patients receiving concomitant treatment with fluoroquinolones, especially in elderly patients. Indeed, careful monitoring blood glucose is recommended in all patients receiving at the same time Gliclazide 80 mg and a fluoroquinolone.

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

Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to hemolytic anemia. Since gliclazide belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**INTERACTIONS WITH OTHER MEDICAMENTS**

The following products are likely to increase the risk of hypoglycaemia:

***Contra-indicated combination***

- Miconazole (systemic route, or mucosal gel): increases the hypoglycaemic effect with possible onset of hypoglycaemic symptoms, or even coma.
- Antibacterial: Sulfonamides may enhance the hypoglycaemic effect of gliclazide.

***Combinations which are not recommended***

- Phenylbutazone (systemic route): increases the hypoglycaemic effect of sulfonylureas (displaces their binding to plasma proteins and/or reduces their elimination). It is preferable to use a different anti-inflammatory agent, or else to warn the patient and emphasize the importance of self- monitoring. Where necessary, adjust the dose during and after treatment with the anti-inflammatory agent.
- Alcohol: increases the hypoglycaemic reaction (by inhibiting compensatory reactions) that can lead to the onset of hypoglycaemic coma. Avoid alcohol or medicines containing alcohol.

***Combinations requiring precautions for use***

Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur when one of the following drugs is taken: other antidiabetic agents (insulins, acarbose, metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists), beta-blockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H2-receptor antagonists, MAOIs, sulfonamides, clarithromycin and nonsteroidal anti- inflammatory agents.

- Anti-gout agents: Enhanced hypoglycemic effect with allopurinol, sulfinpyrazone and probenecid.
- Chloramphenicol: Enhances the hypoglycaemic effect of sulfonylureas
- Beta-blockers: May reduce the hypoglycemic effects of sulphonylureas, and mask the symptoms of hypoglycaemia.
- Fluconazole: May enhance the hypoglycemic effect of sulphonylureas.
- ACE inhibitors: Such as captopril and enalapril, may enhance the hypoglycaemic effect of gliclazide.
- Antimalarial: Possible increase in hypoglycaemia with quinine and quinidine
- Lipid-lowering drugs: Clofibrate group drugs may improve glucose tolerance and have an additive effect.
- Sex hormones, hormone antagonists and steroids: Testosterone and anabolic steroids may enhance the hypoglycaemic effect of gliclazide. Octreotide may cause hypoglycaemia

The following products may cause an increase in blood glucose levels

***Combination which is not recommended***

- Danazol: diabetogenic effect of danazol.

If the use of this active substance cannot be avoided, warn the patient and emphasize the importance of urine and blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic agent during and after treatment with danazol.

***Combinations requiring precautions during use***

- Chlorpromazine (neuroleptic agent): high doses (>100 mg per day of chlorpromazine) increase blood glucose levels (reduced insulin release).Warn the patient and emphasize the importance of blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic active substance during and after treatment with the neuroleptic agent.
- 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). Warn the patient and emphasize the importance of blood glucose monitoring, particularly at the start of treatment. It may be necessary to adjust the dose of the antidiabetic active substance during and after treatment with glucocorticoids.
- Ritodrine, salbutamol, terbutaline: (I.V.) Increased blood glucose levels due to beta-2 agonist effects. Emphasise the importance of monitoring blood glucose levels. If necessary, switch to insulin.
- Saint John's Wort (Hypericum perforatum) preparations: Gliclazide exposure is decreased by Saint John's Wort-Hypericum perforatum. Emphasize the importance of blood glucose levels monitoring.
- Cytotoxic drugs: Crisantaspase may induce hyperglycaemia and the dose of gliclazide may need to be adjusted.
- Antibacterial: Isoniazid may increase blood sugar levels, so the dose of sulphonylurea may need to be adjusted. Rifamycins may reduce the hypoglycaemic effect of sulphonylureas.
- Antihypertensive: Diazoxide may reduce the hypoglycaemic effect of sulphonylureas.
- Antipsychotics: Chlorpromazine in daily doses of 100mg or more can reduce the hypoglycaemic effect of sulphonylureas.
- Diuretics: Loop and thiazide diuretics may reduce the hypoglycaemic effect of sulphonylureas.
- Lithium: May occasionally impair glucose tolerance.
- Sex hormones, hormone antagonists and steroids: Oestrogens, progesterones, oral contraceptives and corticosteroids may reduce the hypoglycaemic effect ofsulphonylureas. Octreotide may cause hyperglycaemia.
- Thyroid hormones: May reduce the effect of sulphonylureas.

***Combination which must be taken into account***

- Anticoagulant therapy (Warfarin):

Sulfonylureas may lead to potentiation of anticoagulationduring concurrent treatment. Adjustment of the anticoagulant may be necessary.

**PREGNANCY AND LACTATION**

***Pregnancy:-***

There is no or limited amount of data from the use of gliclazide in pregnant women, even though there are few data with other sulfonylureas.

Studies in animals have shown reproductive toxicity

As a precautionary measure, it is preferable to avoid the use of Gliclazide during pregnancy.

Control of diabetes should be obtained before the time of conception to reduce the risk of congenital abnormalities linked to uncontrolled diabetes.

Oral hypoglycaemic agents are not suitable; insulin is the drug of first choice for treatment of diabetes during pregnancy. 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 unknown whether gliclazide or its metabolites are excreted in human milk. Given the risk of neonatal hypoglycaemia, the product is therefore contra-indicated in breast-feeding mothers. A risk to the newborns/infants cannot be excluded.

***Fertility:-***

No effect on fertility or reproductive performance was noted in male and female rats

**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 hypoglycemic episode is severe or prolonged, and even if it is temporarily controlled by intake of sugar, immediate medical treatment or even hospitalization is required.

Gastrointestinal disturbances, including abdominal pain, nausea, vomiting dyspepsia, diarrhoea, and constipation have been reported: if these should occur, they can be avoided or minimized 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 anemia, 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 AND 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 hospitalization of the patient. If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid I.V. injection of 50mL of a concentrated glucose solution (20% to 30%). This should be followed by a continuous infusion of a more dilute glucose solution (10%) at a rate necessary to maintain blood glucose levels above 100mg/dl. The patient should be monitored closely for at least 48 hours. Depending on the state of the patient at this time, the doctor should decide whether additional monitoring is required.

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 CONDITION**

Store below 30°C. Protect from light and moisture.

**SHELF LIFE**

Product should not be used beyond the expiry date imprinted on the product packaging.

**INSTRUCTION FOR USE**

RESTRICTED TO ADULTS

As with any hypoglycaemic agent, the dosages should be adjusted to the particular circumstances. In the event of a transitory loss of blood glucose control in a patient where good control is usually achieved by diet, it may be sufficient to administer this product for a short period.

***Patients under the age of 65***

Initial dose:

The recommended initial dose is one tablet per day.

Dosage steps:

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Maintenance treatment:

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Patients at particular risk

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chlorpropamide), they must be closely monitored (for severalweeks). This is to avoid the possible occurrence of hypoglycaemia due to an overlapping of effects from the two treatments.

***Paediatric population:***
The safety and efficacy of gliclazide 80 mg in children and adolescents have not been established. No data are available.

Method of administration: Oral route.

**PACK SIZES**
Blister Pack of 10's tablets:-

- 6 x 10's tablets:
  A PVC/Aluminium blister contain 10 tablets. 6 strip blisters will be packed into the outer carton.
- 10 x 10's tablets:
  A PVC/Aluminium blister contain 10 tablets. 10 strip blisters will be packed into the outer carton.
- 50 x 10's tablets:
  A PVC/Aluminium blister contain 10 tablets. 50 strip blisters will be packed into the outer carton.

**REGISTRATION NUMBER**
MAL20086005AZ

**CONTROLLED MEDICINE**
**UBAT TERKAWAL**

**KEEP MEDICINES OUT OF REACH OF CHILDREN**
**JAUHI UBAT-UBATAN DARI KANAK-KANAK**

For further information, please consult your doctor or your pharmacist.

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| Revision Date | : | 26 Jul 2024 |

Lt-206.01 Product Registration Holder & Manufacturer
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