GLIZID-MR 60 a brand name of Gliclazide modified release tablet is described chemically as [N-[[Hexahydrocyclopenta[c]pyrrol-2(1H)-yl]amino]carbonyl]-4-methylbenzenesulfonamide]. Gliclazide is a second generation sulphonylurea oral hypoglycemic agent used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). It has been recommended for use on the basis of both its metabolic and non metabolic effects.

GLIZID-MR 60 is a white to off white, oval, biconvex uncoated tablet plain on both sides.

COMPOSITION

Each uncoated modified release tablet contains:

Gliclazide BP .............. 60 mg

GLICLAZIDE MODIFIED RELEASE TABLETS

GLIZID - MR 60 has been developed with pharmacokinetic characteristics suited to the Circadian glycemic profile of type 2 diabetes. This approach has been associated with highly favourable results during clinical development. GLIZID - MR 60 allows once daily administration with 24 hour efficacy through progressive delivery of the short acting sulfonylurea gliclazide. Once in contact with gastrointestinal fluid, the hydrophyllic matrix of the tablet expands to form a gel through which gliclazide is released over 24 hours. After morning administration, gliclazide concentration increases during first 6 hours followed by plateau phase, then a progressive reduction over the rest of the day and night. Thus there is a good match between gliclazide levels and the known Circadian variations of glycemia in type 2 diabetes. The modified release preparation shows very high bioavailability which has allowed reduction of the clinical effective gliclazide dose to between 30 and 120 mg/day. Efficient 24 hour blood glucose control is achieved without nocturnal hypoglycemia.

MECHANISM OF ACTION

GLIZID - MR 60 has a high tech formulation which releases the gliclazide in such a manner that the treatment taken once daily with breakfast controls high blood glucose over 24 hours. GLIZID - MR 60 restores the early peak of insulin secretion and ensures glycemic control throughout 24 hours. GLIZID - MR 60 combats microthrombosis by decreasing platelet hyperadhesiveness and hyperaggregation increasing fibrinolytic activity, scavenging free-radicals.

PHARMACOLOGY

Gliclazide reduces blood glucose levels by correcting both defective insulin secretion and peripheral insulin resistance. This occurs by closure of $K^+$ channels in the $\beta$-cells of pancreas,
subsequently calcium channels open, leading to increase in intracellular calcium and induction of insulin release. Gliclazide also increases the sensitivity of β-cells to glucose. Gliclazide also restores peripheral insulin sensitivity, such as decreasing hepatic glucose production, and increasing glucose clearance. Gliclazide also has anti-platelet adhesive activity and reduces levels of free radicals, thereby preventing vascular complications. Gliclazide also has been reported to reduce plasma cholesterol and triglyceride levels after repeated administration.1

PHARMACOKINETICS
Gliclazide MR has been shown to have predictable and reproducible release of gliclazide over a 24 hour period which parallels the 24 hour glycemic profile observed in untreated patients. Gliclazide MR shows linear pharmacokinetics over the 15 to 120 mg dose range in patients with type 2 diabetes mellitus. Fasting C\textsubscript{max} in healthy volunteers given a single 30 mg dose of Gliclazide MR was found to be 0.74 mg / L at a t\textsubscript{max} of 7 hours and AUC was 16.2 mg/L.h. In patients with type 2 diabetes mellitus, the apparent clearance of gliclazide MR was 0.9L/h and apparent volume of distribution (Vd) of 19L. There was an exponential decline in plasma concentration with an elimination half life (t\textsubscript{1/2}) of approximately 16 hours. The drug is highly bound to albumin (35%). It is extensively metabolised to at least seven metabolites; with no active circulating active metabolite. <1% of unchanged gliclazide is excreted in urine.1

Special population
Renal impairment: Mild to moderate renal impairment have not been shown to influence the pharmacokinetic parameters of gliclazide MR significantly.
Effect of food: No significant effect of food on various pharmacokinetic parameters (t\textsubscript{max}, t\textsubscript{1/2}, C\textsubscript{max} and AUC) was observed when gliclazide MR 30 mg was given prior to or 10 minutes after starting breakfast.3

INDICATIONS
Non-insulin dependent diabetes mellitus uncontrolled by diet, exercise and weight.

CONTRAINDICATIONS
Insulin-dependent diabetes mellitus, diabetic coma, precoma and extreme imbalance with tendency to acidosis, hepatic or renal failure, surgical stress or acute infection.2

WARNINGS
Hypoglycemia may occur if the patient's dietary intake is reduced or after accidental or deliberate overdose or after severe exercise, alcohol intake, trauma and stress. Hypoglycemic symptoms can be reduced by prescribing a diabetic meal plan. Immediate intervention should be done if signs and symptoms of hypoglycemia occur.

PRECAUTIONS
Adjust dose of gliclazide according to blood and urinary glucose levels during the first few months. Begin treatment with low doses in patients with renal and/or hepatic impairment.

Usage in pregnancy and lactating women.
Contraindicated.

DRUG INTERACTIONS
Diuretics, barbiturates, phenytoin, rifampicin, corticosteroids, estrogens, estroprogestogens and pure progestogens may reduce the glycemic control. Its hypoglycemic action may be potentiated by salicylates, phenylbutazone, sulphonamides, beta-blockers, clofibric acid, vitamin k antagonist, allopurinol, theophylline, caffeine and monoamine oxidase inhibitors. Concomitant administration of miconazole, perhexiline or cimetidine with gliclazide may result in hypoglycemia. Concomitant administration of gliclazide with agents that increase blood glucose levels should not be considered without careful monitoring of blood glucose levels to avoid hyperglycemia.

ADVERSE REACTIONS
Gastrointestinal disturbances - Nausea, diarrhoea, gastric pain, constipation and vomiting.
Dermatological effects - Rash, pruritus, urticaria, erythema and flushing.

Miscellaneous - Headache and dizziness.

Gliclazide appears to be associated with a low incidence of hypoglycemia. Gliclazide may have the potential to produce adverse cardiovascular effects, however gliclazide has been an established agent for the treatment of NIDDM for a number of years without adverse cardiovascular effects.

OVERDOSAGE AND TREATMENT
Hypoglycemia may occur in case of an overdosage. In the event of an overdosage, gastric lavage should be performed and correction of hypoglycemia attempted by intravenous administration of hypertonic glucose (10 or 30%) with continued monitoring of the patient's blood glucose levels.

DOSAGE AND ADMINISTRATION
The usual daily dose is 1-2 tablets per day as a single dosage. Once daily administration of GLIZID - MR 60 tablet must be taken whole with half-a-glass of water just before breakfast. **The tablet should be swallowed whole and not to be chewed.**

Every administration of GLIZID - MR 60 must be followed by a meal.

STORAGE INSTRUCTIONS
Store at a temperature below 30°C, protect from light and moisture.

REFERENCES