Sensedia®

Tablets
(Glimepiride)

DESCRIPTION
Sensedia® (glimepiride tablets) is an oral blood-glucose-lowering drug of the sulfonylurea class. Glimepiride is a white to yellowish white, crystalline, odorless to practically odorless powder formulated into tablets of 1mg, 2mg, 3mg and 4mg strengths for oral administration. Sensedia® tablets contain the active ingredient glimepiride and the following inactive ingredients: lactose (hydrous), sodium starch glycolate, povidone, microcrystalline cellulose, and magnesium stearate. In addition, Sensedia® 1mg tablets contain Ferric Oxide Red. Sensedia® 2mg tablets contain Ferric Oxide Yellow and FD&C Blue #2 Aluminum Lake, and Sensedia® 4mg tablets contain FD&C Blue #2 Aluminum Lake.
Glimepiride is practically insoluble in water.

CLINICAL PHARMACOLOGY
Mechanism of Action: The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extrapancreatic effects may also play a role in the activity of sulfonylureas such as glimepiride. However, as with other sulfonylureas, the mechanism by which glimepiride lowers blood glucose during long-term administration has not been clearly established. Glimepiride is effective as initial drug therapy. In patients where monotherapy with Glimepiride or metformin has not produced adequate glycemic control, the combination of Glimepiride and metformin may have a synergistic effect, since both agents act to improve glucose tolerance by different primary mechanisms of action. This complementary effect has been observed with metformin and other sulfonylureas, in multiple studies.
Pharmacodynamics: A mild glucose-lowering effect first appeared following single oral doses as low as 0.5-0.6 mg in healthy subjects. The time required to reach the maximum effect (i.e., minimum blood glucose level [T min]) was about 2 to 3 hours. In noninsulin-dependent (Type II) diabetes mellitus (NIDDM) patients, both fasting and 2-hour postprandial glucose levels were significantly lower with glimepiride (1, 2, 4, and 8 mg once daily) than with placebo after 14 days of oral dosing. The glucose-lowering effect in all active treatment groups was maintained over 24 hours. In larger dose-ranging studies, blood glucose and HbA1c were found to respond in a dose-dependent manner over the range of 1 to 4 mg/day of Glimepiride. Some patients, particularly those with higher fasting plasma glucose (FPG) levels, may benefit from doses of Glimepiride up to 8 mg once daily. No difference in response was found when Glimepiride was administered once or twice daily. Glimepiride therapy is effective in controlling blood glucose without deleterious changes in the plasma lipoprotein profiles of patients treated for NIDDM

INDICATIONS AND USAGE
Glimepiride is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with noninsulin-dependent (Type II) diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet and exercise alone. Glimepiride may be used concomitantly with metformin when diet, exercise, and Glimepiride or metformin alone do not result in adequate glycemic control.
Glimepiride is also indicated for use in combination with insulin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic agent.
Combined use of glimepiride and insulin may increase the potential for hypoglycemia. In initiating treatment for noninsulin-dependent diabetes, diet and exercise should be emphasized as the primary 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. In addition to regular physical activity, cardiovascular risk factors should be identified and corrective measures taken where possible.
If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered. Use of Glimepiride must be viewed by both the physician and patient as a treatment in addition to diet and exercise and not as a substitute for diet and exercise 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 Glimepiride.
During maintenance programs, Glimepiride monotherapy should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations. Secondary failures to Glimepiride monotherapy can be treated with Glimepiride-insulin combination therapy.
In considering the use of Glimepiride in asymptomatic patients, it should be recognized that blood glucose control in NIDDM has not definitely been established to be effective in preventing the long-term cardiovascular and neural complications of diabetes However, the Diabetes Control and Complications Trial (DCCT) demonstrated that control of HbAlc and glucose was associated with a decrease in retinopathy, neuropathy, and nephropathy for insulin-dependent diabetic (IDDM) patients.

CONTRAINDICATIONS
Glimepiride is contraindicated in patients with:
- Known hypersensitivity to the drug.
- Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

WARNINGS
SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY
The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. The patient should be informed of the potential risks and advantages of Glimepiride tablets and of alternative modes of therapy.

PRECAUTIONS
General
Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Patients with impaired renal function may be more sensitive to the glucose lowering effect of Glimepiride. A starting dose of 1mg once daily followed by appropriate dose titration is recommended in those patients. Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. Hypoglycemia 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 used. Combined use of glimepiride with insulin or metformin may increase the potential for hypoglycemia.
Loss of control of blood glucose: When a patient stabilized 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 add insulin in combination with Glimepiride or even use insulin monotherapy. The effectiveness of any oral hypoglycemic drug, including Glimepiride, 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. Should secondary failure occur with Glimepiride or metformin monotherapy, combined therapy with Glimepiride and metformin or Glimepiride and insulin may result in a response. Should secondary failure occur with combined Glimepiride/metformin therapy, it may be necessary to initiate insulin therapy.
Information for Patients
Patients should be informed of the potential risks and advantages of Glimepiride and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. The potential for primary and secondary failure should also be explained.
Laboratory Tests
Fasting blood glucose should be monitored periodically to determine therapeutic response. Glycosylated hemoglobin should also be monitored, usually every 3 to 6 months, to more precisely assess long-term glycemic control.
Drug Interactions
The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal anti-inflammatory drugs and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors and beta adrenergic blocking agents. When these drugs are administered to a patient receiving Glimepiride, the patient should be observed closely for hypoglycemia. When these drugs are withdrawn from a patient receiving Glimepiride, the patient should be observed closely for loss of glycemic control.
Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics and isoniazid. When these drugs are administered to a patient receiving Glimepiride, the patient should be closely observed for loss of control. When these drugs are withdrawn from a patient receiving Glimepiride, the patient should be observed closely for hypoglycemia.
Coadministration of aspirin did not affect blood glucose and serum C-peptide concentrations and no hypoglycemic symptoms were reported.
Coadministration of either cimetidine (800 mg once daily) or ranitidine (150 mg bid) with a single 4mg oral dose of Glimepiride did not significantly alter the absorption and disposition of glimepiride, and no differences were seen in hypoglycemic symptomatology.
Concomitant administration of propranolol (40 mg tid) and Glimepiride did not have any effect on the pharmacodynamics of glimepiride. If beta-blockers are used, caution should be exercised and patients should be warned about the potential for hypoglycemia.
Concomitant administration of glimepiride tablets (4 mg once daily) did not alter either the pharmacodynamic effects or the pharmacokinetic characteristics of R- and S-warfarin enantiomers following administration of a single dose (25 mg) of racemic warfarin to healthy subjects.
The responses of serum glucose, insulin, C-peptide, and plasma glucagon to 2 mg Glimepiride were unaffected by coadministration of ramipril (an ACE inhibitor) 5 mg once daily in normal subjects. No hypoglycemic symptoms

were reported.
A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. Potential interactions of glimepiride with other drugs metabolized by cytochrome P450 also include phenytoin, fluconazole, rifampicin, diclofenac, ibuprofen, naproxen, and mefenamic acid.
Although no specific interaction studies were performed, pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of calcium-channel blockers, estrogens, fibrates, NSAIDS, HMG CoA reductase inhibitors, sulfonamides, thyroid hormone or Ace inhibitors.

Pregnancy
Teratogenic Effects:
Pregnancy category C: There are no adequate and well-controlled studies in pregnant women. On the basis of results from animal studies, Glimepiride should not be used during pregnancy.
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 glucose levels as close to normal as possible. Prolonged severe hypoglycemia (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. Patients who are planning a pregnancy should consult their physician, and it is recommended that they change over to insulin for the entire course of pregnancy and lactation.

Nursing Mothers
Although it is not known whether Glimepiride is excreted in human milk, other sulfonylureas are excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, and because of the effects on nursing animals, Glimepiride should be discontinued in nursing mothers. If Glimepiride is discontinued, and if diet and exercise alone are inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
No overall differences in safety or effectiveness were observed between elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. The drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Elderly patients are particularly susceptible to hypoglycemic action of glucose-lowering drugs. In elderly, debilitated, or malnourished patients, or in patients with renal and hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative based upon blood glucose levels prior to and after initiation of treatment to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents.

ADVERSE REACTIONS
Adverse events, other than hypoglycemia, considered to be possibly or probably related to study drug that occurred in more than 1% of patients treated with Glimepiride are: Dizziness, Asthenia, Headache and Nausea.
Gastrointestinal Reactions
Vomiting, gastrointestinal pain, and diarrhea have been reported, but the incidence in placebo-controlled trials was less than 1%. In rare cases, there may be an elevation of liver enzyme levels. In isolated instances, impairment of liver function (e.g with cholestasis and jaundice), as well as hepatitis, which may also lead to liver failure have been reported with sulfonylureas, including Glimepiride.
Dermatologic Reactions
Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients. These may be transient and may disappear despite continued use of Glimepiride. If those hypersensitivity reactions persist or worsen, the drug should be discontinued. Porphyria cutanea tarda, photosensitivity reactions, and allergic vasculitis have been reported with sulfonylureas.
Hematologic Reactions
Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.
Metabolic Reactions
Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas; however, no cases have yet been reported with Glimepiride (glimepiride tablets). Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. 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 increase release of ADH.
Other Reactions
Changes in accommodation and/or blurred vision may occur with the use of Glimepiride. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated. This condition is also seen in untreated diabetic patients, and may actually be reduced by treatment.

OVERDOSAGE
Overdosage of sulfonylureas, including Glimepiride, can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION
There is no fixed dosage regimen for the management of diabetes mellitus with Glimepiride or any other hypoglycemic agent. The patient's fasting blood glucose and HbA1c must be measured periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of adequate blood glucose lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels should be performed to monitor the patient's response to therapy. Short-term administration of Glimepiride may be sufficient during periods of transient loss of control in patients usually controlled well on diet and exercise.
Usual Starting Dose
The usual starting dose of Glimepiride as initial therapy is 1-2 mg once daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1 mg once daily, and should be titrated carefully. No exact dosage relationship exists between Glimepiride and the other oral hypoglycemic agents. The maximum starting dose of Glimepiride should be no more than 2 mg. Failure to follow an appropriate dosage regimen may precipitate hypoglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy.
Usual Maintenance Dose
The usual maintenance dose is 1 to 4 mg once daily. The maximum recommended dose is 8 mg onedaily. After reaching a dose of 2 mg, dosage increases should be made in increments of no more than 2 mg at 1-2 week intervals based upon the patient's blood glucose response. Long-term efficacy should be monitored by measurement of HbA1c levels, for example, every 3 to 6 months.
Glimepiride-Metformin Combination Therapy
If patients do not respond adequately to the maximal dose of Glimepiride monotherapy, addition of metformin may be considered. With concomitant Glimepiride and metformin therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. However, attempts should be made to identify the minimum effective dose of each drug to achieve this goal. With concomitant Glimepiride and metformin therapy, the risk of hypoglycemia associated with Glimepiride therapy continues and may be increased. Appropriate precautions should be taken.
Glimepiride-Insulin Combination Therapy
Combination therapy with Glimepiride and insulin may also be used in secondary failure patients. The fasting glucose level for instituting combination therapy is in the range of >150 mg/dL in plasma or serum depending on the patient. The recommended Glimepiride dose is 8 mg once daily administered with the first main meal. After starting with low-dose insulin, upward adjustments of insulin can be done approximately weekly as guided by frequent measurements of fasting blood glucose. Once stable, combination-therapy patients should monitor their capillary blood glucose on an ongoing basis, preferably daily. Periodic adjustments of insulin may also be necessary during maintenance as guided by glucose and HbA1c levels.
Specific Patient Populations
Glimepiride tablets is not recommended for use in pregnancy, nursing mothers, or children. In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions.
Patients Receiving Other Oral Hypoglycemic Agents
As with other sulfonylurea hypoglycemic agents, no transition period is necessary when transferring patients to Glimepiride. Patients should be observed carefully (1-2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (e.g., chlorpropamide) to Glimepiride due to potential overlapping of drug effect..

STORAGE CONDITIONS
Store in a dry place below 25°C, protected from light. Do not refrigerate.

Do not use after expiry date.

PRESENTATION
Sensedia ® tablets are available as 1 mg, 2 mg, 3 mg & 4 mg in blister packs of 30's.
Keep Medicament out of reach of children.

Manufactured in Zouk Mosbeh Lebanon by
ALGORITHM S.A.L.
® Registered Trademark
Rev. No. 01/06