PRESCRIBING INFORMATION

APO-CHLORPROPAMIDE

Chlorpropamide Tablets USP

100 mg and 250 mg

Oral Hypoglycemic

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Chlorpropamide Tablets USP
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THERAPEUTIC CLASSIFICATION

Oral Hypogylcemic

ACTIONS AND CLINICAL PHARMACOLOGY

Chlorpropamide is an orally active hypoglycemic agent which reduces blood sugar concentration without affecting glucose tolerance. It probably acts by stimulating insulin secretion in the presence of functioning pancreatic islet tissue.

Chlorpropamide is absorbed readily from the gastrointestinal tract and is bound to plasma proteins. Within 1 hour after a single dose, it is detectable in the blood, and the level reaches a maximum within 2 to 4 hours. It is slowly excreted by the kidneys as unchanged chlorpropamide, 2-hydroxy-chlorpropamide, p-chlorbenzene-sulfonylurea, and other metabolites. The biological half-life of a single dose of chlorpropamide averages about 36 hours. Within 96 hours, 80 to 90% of a single oral dose is excreted in the urine. When the drug is administered daily in the appropriate therapeutic dose, it accumulates in the body until a steady state of equilibrium develops between the amount administered (daily) and the amount eliminated (daily) through metabolism and excretion. This equilibrium is usually reached in about 5 to 7 days and no further accumulation occurs thereafter unless the dosage is excessive.

Chlorpropamide exerts a hypoglycemic effect in normal humans within 1 hour, becoming maximal at 3 to 6 hours and persisting for at least 24 hours.

INDICATIONS AND CLINICAL USE

In mild, stable diabetes mellitus of the maturity-onset (or adult) variety to control hyperglycemia responsive to the drug. It should not be used in those patients who are prone to ketosis or who can be controlled by dietary management and exercise alone or for whom insulin therapy is more appropriate.

CONTRAINDICATIONS

- Known hypersensitivity or allergy to chlorpropamide.
- Unstable and/or insulin dependent diabetes mellitus; ketoacidosis; coma; during stress conditions such as severe infections, trauma or surgery.
- Pregnancy.
- In patients with serious impairment of hepatic, renal or thyroid function.

WARNINGS

Chlorpropamide will not prevent the development of complications peculiar to diabetes mellitus.

Chlorpropamide administration must be considered as treatment in addition to a proper dietary regimen and not as a substitute for diet.

Over a period of time, patients may become progressively less responsive to therapy with oral hypoglycemic agents because of deterioration of their diabetic state. If a loss of adequate blood glucose lowering response to chlorpropamide is detected, discontinue the drug.

PRECAUTIONS

Patient Selection and Follow-Up: Careful selection of patients is important. It is imperative that there be rigid attention to diet, careful adjustment of dosage, instruction of the patient on hypoglycemic reactions and their control as well as regular thorough follow-up examinations.

Since the effects of oral hypoglycemic agents on the vascular changes and other long-term sequelae of diabetes mellitus are not fully known, patients receiving such drugs must be closely observed for both short- and long-term complications. Periodic assessment of cardiovascular, ophthalmic, renal and hepatic status is advisable.

Although chlorpropamide given alone has controlled some patients with mild maturity-onset diabetes of the stable type during the stress of mild infection or minor surgery, insulin therapy is generally essential during intercurrent complications (for example, ketoacidosis, sever trauma, major surgery procedures, severe infections, severe diarrhea, nausea and vomiting). The severity of the diabetes, the nature of the complications, and availability of laboratory facilities determine whether therapy can be continued or should be withdrawn while insulin is being used.

Some epidemiological studies have suggested a trend for all-cause mortality associated with the use of first generation sulfonylurea products such as chlorpropamide and provide a basis for caution and close monitoring, especially in high risk patients.

Hypoglycemic Reactions: Severe hypoglycemia can be induced by all sulfonyurea drugs. Particularly susceptible are elderly subjects, patients with impaired hepatic or renal function, those who are debilitated or malnourished and patients with primary or secondary adrenal insufficiency. Hypoglycemic is more likely to occur when the caloric intake is inadequate or after strenuous or prolonged exercise.

Because of the long biological half-life of chlorpropamide, if the patient becomes hypoglycemic during therapy, withdraw the drug and keep the patient under close supervision for 5 to 6 days. Subsequent reinstitution of chlorpropamide at lower dose levels may be considered.

Hemolytic Anemia: Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because APO-CHLORPROPAMIDE belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered. In post-

marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.

Drug Interactions: As a result of drug interaction, hypoglycemia may be potentiated when a sulfonylurea is used concurrently with agents such as: long-acting sulfonamides, tuberculostatics, phenylbutazone, clofibrate, MAO inhibitors, coumarin derivatives, salicylates, probenecid, or beta-adrenergic blocking agents such as propranolol, anabolic steroids and male sex hormones, ACE inhibitors, insulin and other oral antidiabetics, nonsteroidal anti-inflammatory drugs and other drugs that are highly protein bound, such as azapropazone, sulfonamides (e.g. sulphaphenazole), chloramphenicol, clarithromycin, cyclophosphamide, disopyramide, fenyramidol, fenfluramine, fibrates, fluconazole, fluoxetine, guanethidine, ifosfamide, miconazole, oxyphenbutazone, pentoxifylline (high dose parenteral), probenecid, quinolones, sulfonamide antibiotics, sulfinpyrazone, and tetracycline.

When these drugs are administered to a patient receiving APO-CHLORPROPAMIDE, the patient should be observed closely for hypoglycemia. When these drugs are withdrawn from a patient receiving APO-CHLORPROPAMIDE, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of blood sugar control; these include diuretics (thiazides, furosemide and others), corticosteroids, estrogens, oral contraceptives (estrogen plus progestogen), calcium channel blockers, acetazolamide, diazoxide, epinephrine and other sympathomimetic agents, glucagon, isoniazid, laxatives (after protracted use), phenothiazines, phenytoin, rifampicin, thyroid products and nicotinic acid in pharmacologic doses.

When these drugs are administered to a patient receiving APO-CHLORPROPAMIDE, the patient should be closely observed for loss of glycemic control. When these drugs are withdrawn from a patient receiving APO-CHLORPROPAMIDE, the patient should be observed closely for hypoglycemia.

Barbiturates should be used cautiously in patients receiving an oral hypoglycemic agent, since their action may be prolonged.

Intolerance to alcohol (disulfiram-like reaction: flushing, sensation of warmth, giddiness, nausea, and occasionally tachycardia) may occur in patients treated with a sulfonylurea. This reaction can be prevented by avoiding alcohol.

ADVERSE REACTIONS

The majority of the side effects have been dose-related, transient, and have responded to dose reduction or withdrawal of the medication. However, clinical experience thus far has shown that, as with other sulfonylureas, some side effects associated with hypersensitivity may be severe and deaths have been reported in some instances.

Certain untoward reactions associated with idiosyncrasy or hypersensitivity have occurred, including jaundice, skin eruptions rarely progressing to erythema multiforme and exfoliative dermatitis, and probably depression of formed elements of the blood; these reactions show no direct relationship to the size of the dose. They occur characteristically during the first 6 weeks of therapy. With a few exceptions, these manifestations have been mild and readily reversible on the withdrawal of the drug.

Hypoglycemia (see Precautions): Severe hypoglycemia which mimics acute CNS disorders may occur. Hepatic and/or renal disease, malnutrition, debility, advanced age, alcoholism, adrenal or pituitary insufficiency may be predisposing factors.

Gastrointestinal: Nausea, epigastric fullness and heartburn are common reactions, tend to be dose related and may disappear when dosage is reduced. Cholangiolytic jaundice due to intracanalicular biliary stasis with elevation of serum alkaline phosphatase has been reported rarely. In patients with progressive elevation of serum alkaline phosphatase, chlorpropamide should be discontinued.

Dermatologic: Allergic skin reactions such as pruritus, erythema, urticaria, morbilliform or maculopapular eruptions have been observed. These may subside on continued use of chlorpropamide, but if they persist, discontinue the drug. Porphyria cutanea tarda and photosensitivity reactions have been reported.

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia (see Precautions), aplastic anemia.

Metabolic: Hepatic porphyria, disulfiram-like reactions.

Endocrine: Reduced RAI uptake by the thyroid gland has been reported.

Chlorpropamide on some occasions has caused a reaction similar to the syndrome of inappropriate antidiuretic hormone (ADH) secretion. This is characterized by excessive water retention and hyponatremia, low serum osmolality and high urine osmolality.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms: Overdosage with sulfonylureas may result in hypoglycemia, but it should be noted that the dosage which causes hypoglycemia varies widely, and may be within the accepted therapeutic range in sensitive individuals.

The manifestations of hypoglycemia include sweating, flushing or pallor, numbness, chilliness, hunger, trembling, headache, dizziness, increased pulse rate, palpitations, increase in blood pressure and apprehensiveness in the mild cases. In more severe cases, coma appears. However, symptoms of hypoglycemia are not necessarily as typical as described above and sulfonylureas may cause insidious development of symptoms mimicking cerebrovascular insufficiency.

Treatment: Current medical intervention for the treatment of hypoglycemia should be followed according to the condition of the patient. Physicians should anticipate recurrence of hypoglycemia because of the long duration of action of chlorpropamide; Patients should be closely monitored for a minimum of 24 to 48 hours following apparent clinical recovery.

Octreotide or diazoxide have been used as an adjunct to intravenous dextrose in the management of refractory cases of sulfonylurea-induced hypoglycemia.

Glucagon is generally not recommended as an antidote for chlorpropamide overdose.

Hemodialysis is not effective in removing chlorpropamide.

DOSAGE AND ADMINISTRATION

In diabetic subjects there is no fixed dosage regimen for management of blood glucose levels. Individual determination of the minimum dose that will lower the blood glucose adequately should be made.

If the maximal recommended dose fails to lower blood glucose adequately in patients on initial trail, discontinue chlorpropamide. During the course of therapy a loss of effectiveness may occur. It is advisable to ascertain chlorpropamide's contribution in the control of blood glucose by discontinuing the medication semi-annually or at least annually with careful patient monitoring. If the need for chlorpropamide is not evident, the drug should not be resumed. In some diabetic subjects, short-term chlorpropamide administration may be sufficient during periods of transient loss of blood sugar control.

The total daily dosage is generally taken at a single time each morning with breakfast. Occasionally cases of gastrointestinal intolerance may be relieved by dividing the daily dosage. **A loading or priming dose is not necessary and should not be used**.

Usual Starting Dose: The stable, mild, nonketosis-prone maturity-onset or adult type diabetic should be started on 250 mg daily. Because the geriatric diabetic patient appears to be more sensitive to the hypoglycemic effect of sulfonylurea drugs, older patients should be started on smaller amounts of chlorpropamide in the range of 100 to 125 mg daily.

No transition period is necessary when transferring patients from other oral hypoglycemic agents to chlorpropamide. The other agent may be discontinued abruptly and chlorpropamide started at once in appropriate dosage.

Changeover from Insulin: If a change from insulin to chlorpropamide is desirable in a patient with stable, mild, maturity-onset diabetes, treatment with insulin should be discontinued abruptly or gradually as appropriate. After an insulin-free period of 2 or 3 days it is possible to determine whether any therapy other than dietary regulation and exercise is needed. During this withdrawal and insulin-free interval, the patient's urine should be tested at least 3 times daily for glucose and ketone bodies, and the results monitored carefully. The appearance of significant ketonuria accompanied by glucosuria within 12 to 24 hours after withdrawal of insulin strongly suggests that the patient is ketosis prone and precludes the change from insulin to cholorpropamide.

Five to seven days after the initial therapy, the blood level of chlorpropamide reaches a plateau. Dosage may subsequently be adjusted upward or downward by increments of not more than 50 to 125 mg at intervals of 3 to 5 days to obtain optimal control. More frequent adjustments are usually undesirable.

In most patients the response to chlorpropamide will be evident within an initial trial period of 7 days. Others may require up to 1 month for maximum control. Provided severe loss of control does not intervene, a patient should not be classified as a primary failure unless 4 weeks of therapy have failed to produce a satisfactory response.

Usual Maintenance Dose: Most diabetic patients responsive to chlorpropamide are controlled by approximately 250 mg daily. Many investigators have found that some of these diabetics do well on daily doses of 100 mg or less, bit others may require as much as 500 mg daily for adequate

control. Patients who do not respond completely to 500 mg daily will usually not respond to higher doses.

Maximal Dose: Maintenance doses above 500 mg daily should be avoided.

AVAILABILITYOF DOSAGE FORM

APO-CHLORPROPAMIDE 100 mg: Each white, round, flat faced, scored tablet, engraved "APO" over "100" on one side, contains 100 mg of chlorpropamide. Available in bottles of 100 and 500.

APO-CHLORPROPAMIDE 250 mg: Each white, biconvex, scored, oval, film coated tablet, engraved "APO 250" on one side contains 250 mg of chlorpropamide. Available in bottles of 100 and 1000, in unit dose packages of 100 (10 X 10), and in Apotex Long-Term care unit dose packages (APO-LTC Paks) of 620 (20 X 31) and 700 (20 X 35) tablets.

Stability and Storage Recommendations:
Store at room temperature (15 to 30°C).