PRESCRIBING INFORMATION

TOLBUTAMIDE

Tolbutamide Tablets USP

500 mg

Oral Hypoglycemic

AA PHARMA INC.
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500 mg

THERAPEUTIC CLASSIFICATION

Oral Hypoglycemic

ACTIONS

Tolbutamide reduces blood sugar by stimulating the islet tissue to secrete insulin.

Tolbutamide can be detected in the blood within 30 minutes after oral administration; peak concentrations are reached within 3 to 5 hours. The drug is bound to plasma proteins. Tolbutamide is principally oxidized to form a carboxylated metabolite, butyl-p-carboxyphenylsulfonylurea. The carboxylation occurs in the liver and the kidneys. The metabolite does not appear to have clinically significant hypoglycemic effects. The half-life of tolbutamide is about 5 hours. The metabolism and excretion of tolbutamide may be slowed in patients with impaired renal or hepatic function. Tolbutamide is contraindicated in the presence of liver disease or renal impairment.

INDICATIONS AND CLINICAL USE

To control hyperglycemia in tolbutamide responsive diabetes mellitus of stable, mild, nonketosis prone, maturity onset or adult type which cannot be controlled by proper dietary management and exercise or when insulin therapy is not appropriate.

CONTRAINDICATIONS

- Known hypersensitivity or allergy to tolbutamide.
- Unstable and/or insulin dependent diabetes mellitus; ketoacidosis; coma; during stress conditions such as severe infections, trauma or surgery; in the presence of liver disease or frank jaundice; in the presence of renal impairment; thyrotoxicosis.
- During pregnancy or breast-feeding.

WARNINGS

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

Tolbutamide 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 tolbutamide is detected, the drug should be discontinued.

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, hematologic, renal and hepatic status is advisable.

- In patients stabilized on tolbutamide therapy, loss of blood sugar control may occur in cases of acute intercurrent disease or in stressful situations such as trauma or surgery. Under these conditions discontinuation of tolbutamide and administration of insulin should be considered.
- Some epidemiological studies have suggested a trend for all-cause mortality associated with the use of first generation sulfonylurea products such as tolbutamide and provide a basis for caution and close monitoring, especially in high risk patients.

Hypoglycemic reactions: Severe hypoglycemia can be induced by all sulfonylurea 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. Hypoglycemia is more likely to occur when the caloric intake is inadequate or after strenuous or prolonged exercise.

Hemolytic Anemia: Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because TOLBUTAMIDE 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, halofenate, MAO inhibitors, coumarin derivatives, salicylates, chloramphenicol, phenytoin, probenecid, 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), clarithromycin, cyclophosphamide, disopyramide, fenyramidol, fenfluramine, fibrates, fluconazole, fluoxetine, guanethidine, ifosfamide, miconazole, oxyphenbutazone, pentoxifylline (high dose parenteral), quinolones, sulfonamide antibiotics, sulfinpyrazone, and tetracycline.

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

Pseudoproteinuria: A false positive reaction for albumin in urine may be observed when the acidification after boiling test is used because this procedure can produce a flocculent precipitate of urinary tolbutamide metabolites. Use of the sulfosalicylic acid test for urinary albumin circumvents this problem.

ADVERSE REACTIONS

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. Jaundice has been reported rarely.

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

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia (see Precautions) and aplastic anemia have been noted.

Metabolic: Hepatic porphyria, disulfiram-like reactions have been observed.

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

Symptoms:

Sulfonylurea overdose manifests principally as hypoglycemia, which may be severe and can lead to death. The dosage that causes hypoglycemia varies widely, and may be within the daily dosage range in sensitive individuals. The onset of hypoglycemia after an ingestion may be delayed; hypoglycemic episodes may last for several days, especially in susceptible individuals (e.g., the elderly, malnourished individuals, those with renal or hepatic impairment); and hypoglycemia may recur after an apparent recovery.

The manifestations of hypoglycemia include agitation, confusion, diaphoresis and tachycardia. Severe hypoglycemia may result in seizures and coma. Hypokalemia, hypomagnesemia and their associated arrhythmias may occur. Hypothermia may occur. The symptoms of hypoglycemia may be mistaken for cerebrovascular insufficiency or alcohol intoxication.

Treatment:

Current medical intervention for the treatment of hypoglycemia should be followed according to the condition of the patient. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after 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.

Glugacon is generally not recommended as an antidote for tolbutamide overdose.

Hemodialysis is not effective in removing tolbutamide.

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.

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

New diabetics: Give 1 to 2 g of tolbutamide daily as a single dose in the morning, or divided doses, for 4 weeks or until the patient responds; then adjust the maintenance dose (usually 0.5 to 2 g) to the smallest daily dose required to maintain optimum control. A patient should not be considered a primary failure until he has had a four week therapeutic trial, or clinical findings indicate insulin is essential to proper control.
Generally, a daily dose of 1 to 3 gm of tolbutamide will produce maximal response. Exceeding this is unlikely to increase response.

Changeover from Insulin: If a change from insulin to tolbutamide is contemplated in a patient with stable, mild, maturity-onset diabetes, treatment with insulin should be discontinued for a period of 2 or 3 days to determine whether any therapy other than dietary regulation and exercise is needed. During this 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 by a physician. 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 tolbutamide.

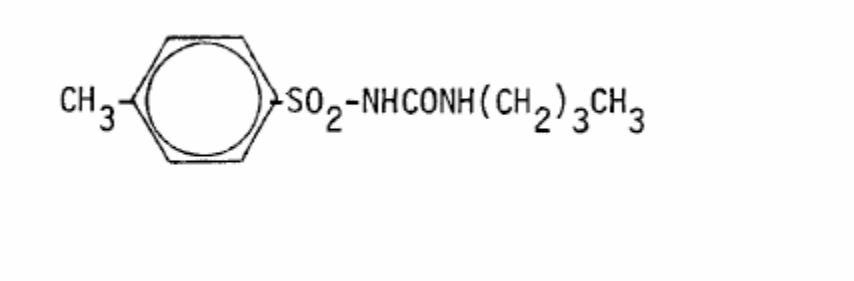
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper/Common Name: Tolbutamide

Chemical Name: 1-Butyl-3-(p-tolylsulfonyl) urea

Structural Formula:



Molecular Formula: $C_{12}H_{18}N_2O_3S$

Molecular Weight: 270.35

Description: Tolbutamide occurs as a white crystalline powder. It is practically odorless and has a slightly bitter taste. It is soluble in alcohol and chloroform and practically insoluble in water.

AVAILABILITYOF DOSAGE FORM

TOLBUTAMIDE 500 mg: Each round, white, biconvex, scored tablet, engraved "TOL", contains tolbutamide 500 mg. Available in bottles of 100 and 1000.

Stability and Storage Recommendations:
Store at room temperature (15 to 30°C) in a tightly closed container.