GLUCOTROL XL®
Extended Release Tablets
For Oral Use

DESCRIPTION
Glipizide is an oral blood-glucose-lowering drug of the sulfonilurea class.

The Chemical Abstracts name of glipizide is 1-cyclohexyl-3-[1-(2-methylpropionamido)cinnamoyl]ethylphenyI]sulfonilureas.
The molecular formula is C₂₇H₃₃N₃O₆S, the molecular weight is 495.58, the structural formula is shown below.

![Chemical Structure of Glipizide](image)

Glipizide is a white, odorless powder with a pKa of 5.9. It is insoluble in water and alcohols, but soluble in 0.1 N NaOH. It is freely soluble in dimethylformamide. GLUCOTROL XL® is a registered trademark for glipizide GITS. Glipizide GITS (Gastrointestinal Therapeutic System) is formulated as a once-a-day controlled release tablet for oral use and is designed to deliver 2.5, 5, or 10 mg of glipizide.

Inert ingredients in the 2.5 mg, 5 mg and 10 mg formulations are: polyethylene oxide, hydroxypropyl methylcellulose, magnesium stearate, sodium chloride, red ferric oxide and sodium hydroxide. The 2.5 mg tablets contain sodium stearate and sodium chloride. Glipizide GITS is available in 2.5 mg, 5 mg and 10 mg tablets with a push button.

The GLUCOTROL XL Extended Release Tablet is designed to provide a controlled rate of delivery of glipizide into the gastrointestinal lumen which is independent of pH or gastrointestinal motility. The function of the GLUCOTROL XL Extended Release Tablet depends upon the existence of an osmotic gradient between the core of the tablet and the GI tract. Drug delivery is essentially constant as long as the osmotic gradient remains constant, and then gradually falls to zero. The logically inert components of the tablet remain intact during GI transit and are eliminated in the feces as an insoluble shell.

Mechanism of Action: Glipizide appears to lower blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. Extrapancreatic effects also may play a part in the mechanism of action of oral sulfonilurea hypoglycemic drugs. Two extrapancreatic effects shown to be important in the action of glipizide are an increase in insulin sensitivity and a decrease in hepatic glucose production. However, the mechanism by which glipizide lowers blood glucose during long-term administration has not been clearly established. Stimulation of insulin secretion by glipizide is an effect dependent upon functioning beta cells in the pancreatic islets. Extrapancreatic effects also may play a part in the mechanism of action of oral sulfonylurea hypoglycemic drugs.
ADVERSE REACTIONS (continued)

Laboratory Tests: The pattern of laboratory test abnormalities observed with glipizide was similar to that for other sulfonylureas. Occasional mild to moderate elevations of SGOT, LDH, alkaline phosphatase, BUN, and creatinine were noted. One case of jaundice was reported. The relationship of these abnormalities to glipizide is uncertain, and they have rarely been associated with clinical symptoms.

OVERDOSAGE

There is no well-documented experience with GLUCOTROL XL overdosage in humans. There have been no known suicide attempts involving GLUCOTROL XL. In animals, signs of hypoglycemia were noted in animals given up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and viral mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility. Pregnancy: Pregnancy Category C: Glipizide was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolmefarad. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of glipizide. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well-controlled studies in pregnant women. Glipizide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 blood-glucose levels as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were given sulfonylureas during the late stages of pregnancy. This has been reported most frequently with agents with prolonged half-lives. If glipizide is used during pregnancy, it should be discontinued at least one month before the expected delivery.

Nursing Mothers: Although it is not known whether glipizide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If the drug is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use: Safety and effectiveness in children have not been established.

Geriatric Use: Of the total number of patients in clinical studies of GLUCOTROL XL, 33 percent were 65 or over. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some individuals cannot be ruled out. Approximately 1-2 days longer were required to reach steady-state in the elderly. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

In U.S. controlled studies the frequency of serious adverse experiences reported was very low and causal relationship has not been established.

The 580 patients from 31 to 87 years of age who received GLUCOTROL XL Extended Release Tablets in doses from 5 mg to 60 mg in both controlled and open trials were included in the evaluation of adverse experiences. All adverse experiences reported were tabulated independently of their possible causal relation to medication.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

Only 3.4% of patients receiving GLUCOTROL XL Extended Release Tablets had hypoglycemia documented by a blood-glucose measurement <60 mg/dL and/or symptoms believed to be associated with hypoglycemia. In a comparative efficacy study of GLUCOTROL XL and Glucotrol, hypoglycemia occurred rarely with an incidence of less than 1% with both drugs.

In double-blind, placebo-controlled studies the adverse experiences reported with an incidence of 3% or more in GLUCOTROL XL-treated patients include:

GLUCOTROL XL (%) Placebo (%)

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>GLUCOTROL XL</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>(N=278)</td>
<td>(N=69)</td>
</tr>
<tr>
<td>10.1</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>8.6</td>
<td>8.7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6.8</td>
<td>7.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.9</td>
<td>7.7</td>
</tr>
<tr>
<td>Tiredness</td>
<td>3.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.6</td>
<td>0.0</td>
</tr>
</tbody>
</table>

The following adverse experiences occurred with an incidence of less than 3% in GLUCOTROL XL-treated patients:

Body as a whole:
- Fatigue
- Phlebitis

Gastrointestinal:
- Nausea
- Vomiting
- Anorexia
- Diarrhea
- Abdominal pain

Respiratory:
- Rhinitis
- Sore throat

Special senses:
- Dizziness
- Tinnitus
- Pruritus

Other:
- Edema
- Weight gain

Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with sulfonylureas.

Urineal-dysuria
- Anuria

Hematologic:
- Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic:
- Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas. In the mouse, glipizide produced a toxic accumulation of acetylaldehyde after oral administration. Clinical experience to date has shown that glipizide has an extremely low incidence of disulfiram-like alcohol reactions.

Endocrine Reactions: Cases of hypogonadism and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with glipizide and other sulfonylureas.

Laboratory Tests: The pattern of laboratory test abnormalities observed with glipizide was similar to that for other sulfonylureas. Occasional mild to moderate elevations of SGOT, LDH, alkaline phosphatase, BUN, and creatinine were noted. One case of jaundice was reported. The relationship of these abnormalities to glipizide is uncertain, and they have rarely been associated with clinical symptoms.