ANTIDIABETIC AGENTS, SULFONYLUREA (Systemic)

Glyburide¾Glibenclamide 7

BAN:

Glyburide¾Glibenclamide 7

JAN:

Glyburide¾Glibenclamide 7

VA CLASSIFICATION (Primary)
Acetohexamide¾HS502
Chlorpropamide¾HS502/CV900
Gliclazide¾HS502
Glimepiride¾HS502
Glipizide¾HS502
Glyburide¾HS502
Tolazamide¾HS502
Tolbutamide¾HS502

Commonly used brand name(s):Albert Glyburide6; Amaryl4; Apo-Chlorpropamide2; Apo-Glyburide6; Apo-Tolbutamide8; DiaBeta6; Diabinese2; Diamicron3; Dimelor1; Dymelor1; Euglucon6; Gen-Glybe6; Glucotrol5; Glucotrol XL5; Glynase PresTab6; Medi-Glybe6; Micronase6; Novo-Butamide8; Novo-Glyburide6; Novo-Propamide2; Nu-Glyburide6; Orinase8; Tolinase7.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

a Not commercially available in the U.S.

b Not commercially available in Canada.

Category

Antidiabetic¾Acetohexamide; Chlorpropamide; Gliclazide; Glimepiride; Glipizide; Glyburide; Tolazamide; Tolbutamide.

Antidiuretic¾Chlorpropamide.

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Diabetes, type 2 (treatment)¾Sulfonylureas are indicated as adjunctive therapy to diet and exercise in the treatment and control of certain patients with type 2 diabetes (previously known as non-insulin-dependent diabetes mellitus [NIDDM], adult-onset diabetes, maturity-onset diabetes, ketosis-resistant diabetes, or stable diabetes), which occurs in individuals who produce or secrete insufficient quantities of endogenous insulin or who have developed resistance to endogenous insulin. 3, 6, 12, 14, 15, 16, 40, 44, 52, 56, 57, 58, 60, 61, 67, 73, 77, 79, 80, 81 An attempt to control diabetes through changes in diet and level of physical activity is usually first-line management before beginning pharmacologic treatment. 3, 6, 12, 14, 15, 16, 40, 52, 56, 57, 60, 61, 62, 78, 80, 81, 82 Patients not responding adequately to diet alone or patients who require diet plus insulin, especially if they require 40 USP Units or less of insulin a day, may be candidates for therapy with a sulfonylurea as monotherapy or combination therapy. 9, 23, 27, 44, 80, 81, 104, 120

Diabetes mellitus, other, associated with certain conditions or syndromes, such as: 61

· Endocrine disease, including endocrine overactivity due to Cushing"s syndrome, hyperthyroidism, pheochromocytoma, somatostatinoma, or aldosteronoma; or endocrine underactivity due to hypoparathyroidism-hypocalcemia, type I isolated growth hormone deficiency, or multitropic pituitary deficiency or 61, 65

· Genetic syndromes, including inborn errors of metabolism, such as glycogen-storage disease type I, or insulin-resistant syndromes, such as muscular dystrophies, late onset proximal myopathy, or Huntington"s chorea. 61, 65

· Sulfonylureas may be used in conditions causing diabetes mellitus induced by hormones, medications, or chemicals in patients who have functioning pancreatic beta cells when the diabetes cannot be controlled by diet or exercise. 61, 65

Combination use of insulin and sulfonylurea agents in patients with type 1 diabetes is controversial because many studies have indicated that sulfonylureas are not effective in the treatment of these patients. 3, 4, 5, 14, 16, 56, 57, 58, 60, 78, 81, 82, 120

Short-term administration of a sulfonylurea or insulin for transient loss of blood glucose control may be sufficient for patients with type 2 diabetes whose blood glucose levels are normally well-controlled with diet. Switching to another sulfonylurea agent may be beneficial if one particular sulfonylurea does not optimally control the diabetes mellitus; however, use of a sulfonylurea should be discontinued if satisfactory reduction of blood glucose concentration is not achieved. 3, 6, 12, 15, 40, 52, 56, 61, 67, 79, 80, 81

The effectiveness of sulfonylureas in controlling blood glucose can decrease over time. 15, 73, 79, 81 If maximum doses of a sulfonylurea fail to control blood glucose, switching to another sulfonylurea or adding metformin to a sulfonylurea treatment regimen may be beneficial in increasing glycemic control and lipoprotein metabolism and may help avoid initiation of insulin therapy. This is especially successful in patients with type 2 diabetes whose blood sugar levels are poorly controlled by insulin alone, in short-term diabetics, or in patients who are 120 to 160% over ideal baseline body weight but who are not excessively insulin-resistant. Glimepiride and metformin may be used concomitantly when diet, exercise and glimepiride or metformin alone do not adequately control blood glucose levels. Combined use of glimepiride and metformin may increase the potential for hypoglycemia. 244 Alternatively, low-dose

insulin in conjunction with sulfonylureas can help to avoid using large doses of insulin, especially for patients with type 2 diabetes who are obese. 2, 4, 5, 11, 20, 21, 22, 23, 24 However, complications, such as weight gain, the effects of hyperinsulinemia, and an increased risk of hypoglycemia need to be considered. 2, 20, 21, 22, 23, 24, 190, 191, 192 Some patients with type 2 diabetes who are nonobese and who are experiencing secondary sulfonylurea failure may be best treated with insulin. 11, 24 A sulfonylurea should be discontinued any time it fails to contribute to the lowering of plasma glucose in a patient for whom compliance with proper diet and sulfonylurea dosing has been determined to be adequate. 15, 24, 80, 81, 192, 193

[Diabetes insipidus, central, partial (treatment)] *¾Chlorpropamide is also indicated as secondary therapy 9 in selected patients to treat partial central diabetes insipidus. Used as an antidiuretic, chlorpropamide has successfully reduced polyuria in about 50% of such treated patients. Chlorpropamide may be used alone or in combination with another agent such as carbamazepine or clofibrate so that the dose of both can be reduced and side effects minimized. Desmopressin is considered the primary treatment for diabetes insipidus. 9

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to one of the sulfonylureas may be sensitive to the others also; cross-sensitivity to other sulfonamide- or thiazide-type medications may also occur. 11

Carcinogenicity

Acetohexamide¾Long-term studies in rats and mice showed no evidence of carcinogenicity. 3

Chlorpropamide¾Chronic toxicity studies in dogs treated for 6, 13, and 20 months with doses of chlorpropamide greater than 20 times the human dose showed no histological or pathological abnormalities. 6

Gliclazide¾Specific carcinogenicity studies have not been done in animals; however, long-term toxicity studies have not shown any evidence of drug-related carcinogenicity.

Glimepiride¾A 24-month study in rats given doses approximately 340 times the maximum recommended human dose based on body surface area showed no evidence of carcinogenicity. 44

Glipizide¾Large-dose studies using up to 75 times the maximum human dose in rats and in mice for 20 and 18 months, respectively, showed no evidence of drug-related carcinogenicity. 14, 52, 80

Glyburide¾An 18-month study in rats given doses of up to 300 mg per kg of body weight (mg/kg) a day and a 2-year oncogenicity study in mice showed no evidence of drug-related carcinogenicity. 12, 40, 73, 81

Tolazamide¾A 103-week study in rats and mice at both low and high doses showed no evidence of carcinogenicity. 15

Tolbutamide¾A 78-week study in male and female rats and mice showed no evidence of carcinogenicity. 16

Mutagenicity

Acetohexamide¾Sister chromatid exchange testing showed no evidence of mutagenicity. 3

Chlorpropamide¾The micronucleus test in one strain of Swiss mice given chlorpropamide doses of 200, 400, 800, and 1600 mg/kg (32 times greater than the therapeutic adult dose) showed no evidence of mutagenicity. 36 However, three strains of mice showed positive results when evaluated using the Salmonella /microsome test. The results are questionable because negative results were also shown in rats and Chinese hamsters. Although an increase in chromosomal breakage has not been observed in treated mammals, Chinese hamsters, rats, or mice, the sister chromatin exchange showed a positive reaction with Chinese hamster cells in vivo and in vitro ; however, spontaneous breakage in this study was not even doubled in extremely high doses. It is difficult to assign a cause-and-effect explanation to the slightly positive results in these animal studies. 36, 37

Gliclazide¾The Ames test, human lymphocyte test, and micronucleus test did not reveal mutagenicity.

Glimepiride¾A series of in vitro and in vivo studies, including the Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, and mouse micronucleus test, showed no evidence of mutagenicity. 44

Glipizide¾Bacterial and in vivo mutagenicity testing showed no evidence of mutagenicity. 14, 52, 80

Glyburide¾Testing with the Ames test, DNA damage/alkaline elution assay, and the micronucleus test (at doses 60 to 240 times the average human therapeutic dose) showed no evidence of mutagenicity. 12, 37, 38, 40, 73, 81

Tolbutamide¾The Ames test 16 and the micronucleus test in mice (at doses of 500 mg/kg) showed no evidence of mutagenicity. 38

Pregnancy/Reproduction

Fertility¾Acetohexamide, tolazamide, tolbutamide¾ Studies in humans have not been done.
Studies in animals have not been done. 3, 16

Chlorpropamide¾ Studies in humans have not been done. 6

Studies in rats treated with high doses of chlorpropamide (125 mg/kg) for 6 to 12 months showed varying degrees of spermatogenesis suppression. 6

Gliclazide¾ Studies in humans have not been done.
Studies in female rats and the first generation offspring of treated male and female rats showed no evidence of impaired fertility.

Glimepiride¾ Studies in humans have not been done. 44

Studies in male mice and male and female rats given more than 1700 times and approximately 4000 times, respectively, the maximum recommended human dose based on body surface area showed no evidence of impaired fertility. 44

Glipizide¾ Studies in humans have not been done. 14

Studies in male and female rats given 75 times the maximum human dose showed no evidence of impaired fertility. 14, 80

Glyburide¾ Studies in humans have not been done. 12, 73, 81

FDA Pregnancy Category C. 44

Glipizide¾ Studies in humans have not been done. Glipizide should be discontinued at least 1 month before the expected delivery date. 14, 52, 80

Studies in rats have shown glipizide to be fetotoxic at all doses from 5 to 50 mg/kg; the fetotoxicity is thought to be due to the pharmacologic hypoglycemic effect during the perinatal period. 14, 52, 80 No teratogenic effects were found in studies in rats and rabbits. 14, 52, 80

FDA Pregnancy Category C. 14, 52, 80

Glyburide¾ Glyburide does not significantly cross the placenta according to an in vitro study using human placentas. 51 Studies in humans have not been done. Use should be discontinued at least 2 weeks before the expected delivery date. 12, 40, 73, 81

Studies in rats and rabbits given up to 500 times the human dose have produced no evidence of teratogenicity. 40, 81

FDA Pregnancy Category B (Micronase, Glynase PresTab). 40, 73, 81

FDA Pregnancy Category C (DiaBeta). 12

Tolazamide¾ Studies in humans have not been done. Use should be discontinued at least 2 weeks before the expected delivery date. 15

Studies in rats given 10 times the human dose have shown tolazamide to cause reduced litter sizes. No teratogenic effects were found. High doses of 100 mg/kg a day also produced reduced litter sizes and increased perinatal mortality in pups. 15

FDA Pregnancy Category C. 15

Tolbutamide¾ Studies in humans have not been done. Use should be discontinued at least 2 weeks before the expected delivery date. 16

Studies in rats given doses of tolbutamide that were 25 to 100 times greater than the human dose have shown teratogenic effects, such as ocular and bone abnormalities, and increased mortality in the offspring. 16, 27, 49 Repeat studies in rabbits showed no teratogenic effects. 16, 45, 49

FDA Pregnancy Category C. 16

Delivery¾Prolonged severe hypoglycemia lasting for 4 to 10 days has been reported in neonates born to mothers who were receiving a sulfonylurea antidiabetic agent at the time of delivery. This effect has been reported more frequently with those agents with longer half-lives, such as chlorpropamide. 3, 6, 14, 15, 16, 44, 49, 55, 65, 80 If sulfonylureas are used during pregnancy, they should be discontinued according to the manufacturer's labeling.

Breast-feeding

Chlorpropamide and tolbutamide are distributed into human breast milk and potentially may cause hypoglycemia in the infant. Glimepiride is distributed into the milk of rats. 44 It is not known whether acetohexamide, gliclazide, glipizide, glyburide, or tolazamide is distributed into breast milk. 3, 12, 14, 15, 16, 40, 52, 53, 65, 73, 79, 80, 81

Chlorpropamide: 33 Chlorpropamide has been found to be distributed into breast milk at a concentration of 5 mcg per mL after 5 hours for a single 500-mg dose (after 5 hours, blood concentration for a single dose of 250 mg chlorpropamide is 30 mcg per mL); therefore, its use during breast-feeding is not recommended. 6 Its effect on the nursing infant is not known. 53

Glimepiride: Glimepiride is distributed into the milk of rats in significant concentrations. The offspring of rats exposed to high concentrations during pregnancy developed skeletal abnormalities after nursing. Use of glimepiride during breast-feeding is not recommended. 44

Tolbutamide: Tolbutamide was distributed into breast milk at a concentration averaging 3 and 18 mcg per mL in two patients taking 500 mg twice a day (milk:plasma ratio of 0.09 and 0.4, respectively). The effect on the nursing infants is not known. The American Academy of Pediatrics considers tolbutamide to be compatible with breast-feeding. 53, 64

Pediatrics

Oral antidiabetic agents are not effective in type 1 (juvenile-onset) diabetes. Because type 2 diabetes occurs rarely in this age group, very little or no published pediatrics-specific information is available. Safety and efficacy have not been established. 3, 6, 12, 14, 16, 40, 44, 52, 65, 73, 79, 80, 81

Geriatrics

In general, no overall difference in safety or efficacy was apparent in persons over 65 years of age when compared to persons younger than 65 years of age taking sulfonylureas for type 2 diabetes. 44, 80 Lower doses are used initially because of possible increased sensitivity to these agents due to age-related metabolism and excretion changes; the steady state concentration of extended-release glipizide has been delayed for 1 or 2 days in elderly patients. 31, 80, 96 The risk of adverse reactions is relatively low when other factors for toxicity, including liver and kidney disease and known drug interactions, are considered. Special counseling with emphasis on hydration, diet, and exercise may be necessary because of the greater risk of hypoglycemia in this age group. Special instruction to recognize hypoglycemia may be needed because early warning adrenergic symptoms of hypoglycemia (such as sweating, weakness, tachycardia, and nervousness) are absent in many patients. Hypoglycemia

manifests as neurological symptoms (such as headache, irritability, mental confusion, unusual tiredness, and drowsiness) and may be more prolonged and severe in the elderly. Combining antidiabetic agents (sulfonylureas with metformin or insulin) or using long-acting sulfonylureas, such as chlorpropamide and glyburide, is most often associated with hypoglycemia in elderly patients and is not generally recommended; 55 shorter-acting sulfonylureas cause fewer problems. Also, instructions may be needed to help the patient monitor urine or blood glucose if visual problems are present. 30, 31, 78, 96

Geriatric patients may be more likely to develop a reversible syndrome of inappropriate antidiuretic hormone (SIADH) from the use of chlorpropamide. The incidence of SIADH is rare and occurs with greater incidence when thiazides are taken concurrently with chlorpropamide than when chlorpropamide is taken alone (10% versus 3%, respectively). In one study, women over 70 years of age were affected 10 times more often than women under 60 years of age when thiazides were used concurrently with chlorpropamide. It is not thought to be a gender-oriented effect. SIADH has been rarely reported with tolbutamide. 99, 100

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

There is an increased chance of hypoglycemia occurring if more than one hypoglycemia-causing agent is used concurrently with sulfonylureas. 12, 16, 58, 52, 60, 80, 81 If the need exists to administer any medications that may affect metabolic or glycemic control of type 2 diabetes, blood glucose concentrations should be monitored by the patient or health care professional. This is particularly important when any medication is added to or removed from an established drug regimen. Subsequent adjustments in diet or antidiabetic agent dosage or both may be necessary; these adjustments may differ depending on the severity of the diabetes. 97

>> Alcohol 6, 9, 12, 17, 30, 40, 56, 57, 58, 60, 65, 67, 73, 77, 79, 81, 99, 101, 118, 123

(a disulfiram-like reaction, which is characterized primarily by flushing of the face, neck, and arms, may occur with any of the sulfonylureas when alcohol is ingested concurrently but has not been reported with glipizide; risk is lowest with tolbutamide and glyburide and highest with chlorpropamide; it has occurred 12 hours after a single 250-mg dose of chlorpropamide and 40 mL of 18% alcohol 17, 56, 57, 58, 118, 119, 123 )

(the risk of hypoglycemia may be increased or prolonged when moderate or large amounts of alcohol have been consumed concurrently with sulfonylurea antidiabetic agents; 121, 122 small amounts of alcohol taken with meals do not usually result in hypoglycemia 17, 62, 101, 124 )

Allopurinol

(increased risk of hypoglycemia due to inhibition of renal tubular secretion of chlorpropamide; closer monitoring required 125 )