

GLIMEPIRIDE- glimepiride tablet
Northwind Pharmaceuticals, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GLIMEPIRIDE TABLETS safely and effectively. See full prescribing information for GLIMEPIRIDE TABLETS.

GLIMEPIRIDE tablets for oral use

Initial U.S. Approval: 1995

INDICATIONS AND USAGE

Glimepiride is a sulfonylurea indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1)

Limitations of Use:

- Not for treating type 1 diabetes mellitus or diabetic ketoacidosis (1)

DOSAGE AND ADMINISTRATION

- Recommended starting dose is 1 or 2 mg once daily. Increase in 1 or 2 mg increments no more frequently than every 1 to 2 weeks based on glycemic response. Maximum recommended dose is 8 mg once daily. (2.1)
- Administer with breakfast or first meal of the day. (2.1)
- Use 1 mg starting dose and titrate slowly in patients at increased risk for hypoglycemia (e.g., elderly, patients with renal impairment). (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets (scored): 1 mg, 2 mg, 4 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to glimepiride or any of the product's ingredients (4)
- Hypersensitivity to sulfonamide derivatives (4)

WARNINGS AND PRECAUTIONS

- Hypoglycemia: May be severe. Ensure proper patient selection, dosing, and instructions, particularly in at-risk populations (e.g., elderly, renally impaired) and when used with other anti-diabetic medications (5.1).
- Hypersensitivity Reactions: Postmarketing reports include anaphylaxis, angioedema and Stevens-Johnson Syndrome. If a reaction is suspected, promptly discontinue glimepiride, assess for other potential causes for the reaction, and institute alternative treatment for diabetes. (5.2).
- Hemolytic Anemia: Can occur if glucose 6-phosphate dehydrogenase (G6PD) deficient. Consider a non-sulfonylurea alternative. (5.3).
- Potential Increased Risk of Cardiovascular Mortality with Sulfonylureas: Inform patient of risks, benefits and treatment alternatives. (5.4).
- Macrovascular Outcomes: No clinical studies establishing conclusive evidence of macrovascular risk reduction with glimepiride or any other anti-diabetic drug (5.5).

ADVERSE REACTIONS

Common adverse reactions in clinical trials ($\geq 5\%$ and more common than with placebo) include hypoglycemia, headache, nausea, and dizziness (6.1). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Accord Healthcare Inc. at 1-866-941-7875 or www.accordhealthcare.us or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch . (6)

DRUG INTERACTIONS

- Certain medications may affect glucose metabolism, requiring glimepiride dose adjustment and close monitoring of blood glucose. (7.1).
- Miconazole: Severe hypoglycemia can occur when glimepiride and oral miconazole are used concomitantly (7.2).
- Cytochrome P450 2C9 interactions: Inhibitors and inducers of cytochrome P450 2C9 may affect glycemic control by altering glimepiride plasma concentrations. (7.3).
- Colesevelam: Coadministration may reduce glimepiride absorption. Glimepiride should be administered at least 4 hours prior to colesevelam (2.1, 7.4).

USE IN SPECIFIC POPULATIONS

- Pediatric Patients: Not recommended because of adverse effects on body weight and hypoglycemia (

8.4). (8)

· Geriatric or Renally Impaired Patients: At risk for hypoglycemia with glimepiride. Use caution in dose selection and titration, and monitor closely (8.5, 8.6). (8)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Hypoglycemia

5.2 Hypersensitivity Reactions

5.3 Hemolytic Anemia

5.4 Increased Risk of Cardiovascular Mortality with Sulfonylureas

5.5 Macrovascular Outcomes

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

7.1 Drugs Affecting Glucose Metabolism

7.2 Miconazole

7.3 Cytochrome P450 2C9 Interactions

7.4 Concomitant Administration of Colesevelam

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

14 CLINICAL STUDIES

14.1 Monotherapy

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Glimepiride tablets are indicated as an adjunct to diet and exercise to improve glycemic

control in adults with type 2 diabetes mellitus [see *Clinical Studies* (14.1)].

Limitations of Use

Glimepiride tablets should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Glimepiride tablets should be administered with breakfast or the first main meal of the day.

The recommended starting dose of glimepiride tablet is 1 mg or 2 mg once daily. Patients at increased risk for hypoglycemia (e.g., the elderly or patients with renal impairment) should be started on 1 mg once daily [see *Warnings and Precautions* (5.1) and *Use in Specific Populations* (8.5, 8.6)].

After reaching a daily dose of 2 mg, further dose increases can be made in increments of 1 mg or 2 mg based upon the patient's glycemic response. Uptitration should not occur more frequently than every 1 to 2 weeks. A conservative titration scheme is recommended for patients at increased risk for hypoglycemia [see *Warnings and Precautions* (5.1) and *Use in Specific Populations* (8.5, 8.6)].

The maximum recommended dose is 8 mg once daily.

Patients being transferred to glimepiride from longer half-life sulfonylureas (e.g., chlorpropamide) may have overlapping drug effect for 1 to 2 weeks and should be appropriately monitored for hypoglycemia.

When colesevelam is coadministered with glimepiride, maximum plasma concentration and total exposure to glimepiride is reduced. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

3 DOSAGE FORMS AND STRENGTHS

Glimepiride tablets, USP are formulated as tablets of:

- 1 mg tablets (pink coloured, oval shaped, biconvex, uncoated tablets debossed with 'AHI 1' on one side and break line on the other)
- 2 mg tablets (green coloured, oval shaped, biconvex, uncoated tablets debossed with 'AHI 2' on one side and break line on the other)
- 4 mg tablets (blue coloured, oval shaped, biconvex, uncoated tablets debossed with 'AHI 4' on one side and break line on the other)

4 CONTRAINDICATIONS

Glimepiride tablet is contraindicated in patients with a history of a hypersensitivity reaction to:

- Glimepiride or any of the product's ingredients [see *Warnings and Precautions* (5.2)].
- Sulfonamide derivatives: Patients who have developed an allergic reaction to sulfonamide derivatives may develop an allergic reaction to glimepiride. Do not use

glimepiride in patients who have a history of an allergic reaction to sulfonamide derivatives.

5 WARNINGS AND PRECAUTIONS

5.1 Hypoglycemia

All sulfonylureas, including glimepiride, can cause severe hypoglycemia [see *Adverse Reactions* (6.1)]. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. These impairments may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death.

Patients must be educated to recognize and manage hypoglycemia. Use caution when initiating and increasing glimepiride doses in patients who may be predisposed to hypoglycemia (e.g., the elderly, patients with renal impairment, patients on other anti-diabetic medications). Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic impairment are particularly susceptible to the hypoglycemic action of glucose-lowering medications. Hypoglycemia is also more likely to occur when caloric intake is deficient, after severe or prolonged exercise, or when alcohol is ingested.

Early warning symptoms of hypoglycemia may be different or less pronounced in patients with autonomic neuropathy, the elderly, and in patients who are taking beta-adrenergic blocking medications or other sympatholytic agents. These situations may result in severe hypoglycemia before the patient is aware of the hypoglycemia.

5.2 Hypersensitivity Reactions

There have been postmarketing reports of hypersensitivity reactions in patients treated with glimepiride, including serious reactions such as anaphylaxis, angioedema, and Stevens-Johnson Syndrome [see *Adverse Reactions* (6.2)]. If a hypersensitivity reaction is suspected, promptly discontinue glimepiride, assess for other potential causes for the reaction, and institute alternative treatment for diabetes.

5.3 Hemolytic Anemia

Sulfonylureas can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Because glimepiride is a sulfonylurea, use caution in patients with G6PD deficiency and consider the use of a non-sulfonylurea alternative. There are also postmarketing reports of hemolytic anemia in patients receiving glimepiride who did not have known G6PD deficiency [see *Adverse Reactions* (6.2)].

5.4 Increased Risk of Cardiovascular Mortality with Sulfonylureas

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. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups.

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2 and a half times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glimepiride and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

5.5 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with glimepiride or any other anti-diabetic drug.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in more detail below and elsewhere in the labeling:

Hypoglycemia [see Warnings and Precautions (5.1)]

Hemolytic anemia [see Warnings and Precautions (5.3)]

7 DRUG INTERACTIONS

7.1 Drugs Affecting Glucose Metabolism

A number of medications affect glucose metabolism and may require glimepiride dose adjustment and particularly close monitoring for hypoglycemia or worsening glycemic control.

The following are examples of medications that may increase the glucose-lowering effect of sulfonylureas including glimepiride, increasing the susceptibility to and/or intensity of hypoglycemia: oral anti-diabetic medications, pramlintide acetate, insulin, angiotensin converting enzyme (ACE) inhibitors, H₂ receptor antagonists, fibrates, propoxyphene, pentoxifylline, somatostatin analogs, anabolic steroids and androgens, cyclophosphamide, phenylramidol, guanethidine, fluconazole, sulfapyrazone, tetracyclines, clarithromycin, disopyramide, quinolones, and those drugs that are highly protein-bound, such as fluoxetine, nonsteroidal anti-inflammatory drugs, salicylates, sulfonamides, chloramphenicol, coumarins, probenecid and monoamine oxidase inhibitors. When these medications are administered to a patient receiving glimepiride, monitor the patient closely for hypoglycemia. When these medications are withdrawn from a patient receiving glimepiride, monitor the patient closely for worsening glycemic control.

The following are examples of medications that may reduce the glucose-lowering effect

of sulfonylureas including glimepiride, leading to worsening glycemic control: danazol, glucagon, somatropin, protease inhibitors, atypical antipsychotic medications (e.g., olanzapine and clozapine), barbiturates, diazoxide, laxatives, rifampin, thiazides and other diuretics, corticosteroids, phenothiazines, thyroid hormones, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics (e.g., epinephrine, albuterol, terbutaline), and isoniazid. When these medications are administered to a patient receiving glimepiride, monitor the patient closely for worsening glycemic control. When these medications are withdrawn from a patient receiving glimepiride, monitor the patient closely for hypoglycemia.

Beta-blockers, clonidine, and reserpine may lead to either potentiation or weakening of glimepiride's glucose-lowering effect.

Both acute and chronic alcohol intake may potentiate or weaken the glucose-lowering action of glimepiride in an unpredictable fashion.

The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

7.2 Miconazole

A potential interaction between oral miconazole and sulfonylureas leading to severe hypoglycemia has been reported. Whether this interaction also occurs with other dosage forms of miconazole is not known.

7.3 Cytochrome P450 2C9 Interactions

There may be an interaction between glimepiride and inhibitors (e.g., fluconazole) and inducers (e.g., rifampin) of cytochrome P450 2C9. Fluconazole may inhibit the metabolism of glimepiride, causing increased plasma concentrations of glimepiride which may lead to hypoglycemia. Rifampin may induce the metabolism of glimepiride, causing decreased plasma concentrations of glimepiride which may lead to worsening glycemic control.

7.4 Concomitant Administration of Colesevelam

Colesevelam can reduce the maximum plasma concentration and total exposure of glimepiride when the two are coadministered. However, absorption is not reduced when glimepiride is administered 4 hours prior to colesevelam. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

8 USE IN SPECIFIC POPULATIONS

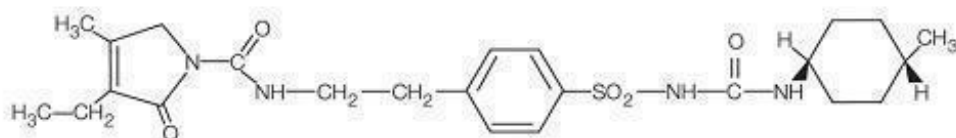
10 OVERDOSAGE

An overdose of glimepiride, as with other sulfonylureas, can produce severe hypoglycemia. Mild episodes of hypoglycemia can be treated with oral glucose. Severe hypoglycemic reactions constitute medical emergencies requiring immediate treatment. Severe hypoglycemia with coma, seizure, or neurological impairment can be treated with glucagon or intravenous glucose. Continued observation and additional carbohydrate intake may be necessary because hypoglycemia may recur after apparent clinical recovery [see *Warnings and Precautions* (5.1)]

11 DESCRIPTION

Glimepiride is an oral sulfonylurea that contains the active ingredient glimepiride. Chemically, glimepiride is identified as 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea (C₂₄H₃₄N₄O₅S) with a molecular weight of 490.62. Glimepiride is a white to yellowish-white, crystalline, odorless to practically odorless powder and is practically insoluble in water.

The structural formula is:



Glimepiride tablets, USP contain the active ingredient glimepiride and the following inactive ingredients: lactose monohydrate, sodium starch glycolate, povidone, and magnesium stearate. In addition, glimepiride tablets, USP 1 mg contain ferric oxide red, glimepiride tablets, USP 2 mg contain ferric oxide yellow and FD &C blue #2 aluminum lake, and glimepiride tablets, USP 4 mg contain FD&C blue #2 aluminum lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Glimepiride primarily lowers blood glucose by stimulating the release of insulin from pancreatic beta cells. Sulfonylureas bind to the sulfonylurea receptor in the pancreatic beta-cell plasma membrane, leading to closure of the ATP-sensitive potassium channel, thereby stimulating the release of insulin.

12.2 Pharmacodynamics

In healthy subjects, the time to reach maximal effect (minimum blood glucose concentrations) was approximately 2 to 3 hours after single oral doses of glimepiride. The effects of glimepiride on HbA_{1c}, fasting plasma glucose, and postprandial glucose have been assessed in clinical trials [see *Clinical Studies* (14)].

12.3 Pharmacokinetics

Absorption : Studies with single oral doses of glimepiride in healthy subjects and with multiple oral doses in patients with type 2 diabetes showed peak drug concentrations (C_{max}) 2 to 3 hours postdose. When glimepiride was given with meals, the mean C_{max} and AUC (area under the curve) were decreased by 8% and 9%, respectively.

Glimepiride does not accumulate in serum following multiple dosing. The

pharmacokinetics of glimepiride does not differ between healthy subjects and patients with type 2 diabetes. Clearance of glimepiride after oral administration does not change over the 1 mg to 8 mg dose range, indicating linear pharmacokinetics.

In healthy subjects, the intraindividual and interindividual variabilities of glimepiride pharmacokinetic parameters were 15% to 23% and 24% to 29%, respectively.

Distribution: After intravenous dosing in healthy subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

Metabolism: Glimepiride is completely metabolized by oxidative biotransformation after either an intravenous or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 is involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M2 is inactive. In animals, M1 possesses about one-third of the pharmacological activity of glimepiride, but it is unclear whether M1 results in clinically meaningful effects on blood glucose in humans.

Excretion: When ¹⁴C-glimepiride was given orally to 3 healthy male subjects, approximately 60% of the total radioactivity was recovered in the urine in 7 days. M1 and M2 accounted for 80% to 90% of the radioactivity recovered in the urine. The ratio of M1 to M2 in the urine was approximately 3:2 in two subjects and 4:1 in one subject. Approximately 40% of the total radioactivity was recovered in feces. M1 and M2 accounted for about 70% (ratio of M1 to M2 was 1:3) of the radioactivity recovered in feces. No parent drug was recovered from urine or feces. After intravenous dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite was observed.

Specific Populations

Geriatric patients:

A comparison of glimepiride pharmacokinetics in patients with type 2 diabetes ≤ 65 years and those > 65 years was evaluated in a multiple-dose study using glimepiride 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the two age groups. The mean AUC at steady state for the older patients was approximately 13% lower than that for the younger patients; the mean weight-adjusted clearance for the older patients was approximately 11% higher than that for the younger patients.

Gender: There were no differences between males and females in the pharmacokinetics of glimepiride when adjustment was made for differences in body weight.

Race: No studies have been conducted to assess the effects of race on glimepiride pharmacokinetics but in placebo-controlled trials of glimepiride in patients with type 2 diabetes, the reduction in HbA1C was comparable in Caucasians (n = 536), blacks (n = 63), and Hispanics (n = 63).

Renal impairment: In a single-dose, open-label study glimepiride 3 mg was administered to patients with mild, moderate and severe renal impairment as estimated by creatinine clearance (CL_{cr}): Group I consisted of 5 patients with mild renal impairment (CL_{cr} > 50 mL/min), Group II consisted of 3 patients with moderate renal impairment (CL_{cr} = 20 to 50 mL/min) and Group III consisted of 7 patients with severe renal impairment (CL_{cr} < 20 mL/min). Although glimepiride serum concentrations decreased with decreasing renal function, Group III had a 2.3-fold higher mean AUC for M1 and an 8.6-fold higher mean AUC for M2 compared to corresponding mean AUCs in Group I.

The apparent terminal half-life ($T_{1/2}$) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as a percentage of dose decreased from 44.4% for Group I to 21.9% for Group II and 9.3% for Group III.

Hepatic impairment: It is unknown whether there is an effect of hepatic impairment on glimepiride pharmacokinetics because the pharmacokinetics of glimepiride has not been adequately evaluated in patients with hepatic impairment.

Obese patients: The pharmacokinetics of glimepiride and its metabolites were measured in a single-dose study involving 28 patients with type 2 diabetes who either had normal body weight or were morbidly obese. While the t_{max} , clearance and volume of distribution of glimepiride in the morbidly obese patients were similar to those in the normal weight group, the morbidly obese had lower C_{max} and AUC than those of normal body weight. The mean C_{max} , AUC_{0-24} , $AUC_{0-\infty}$ values of glimepiride in normal vs. morbidly obese patients were 547 ± 218 ng/mL vs. 410 ± 124 ng/mL, 3210 ± 1030 hours•ng/mL vs. 2820 ± 1110 hours•ng/mL and 4000 ± 1320 hours•ng/mL vs. 3280 ± 1360 hours•ng/mL, respectively.

Drug Interactions:

Aspirin: In a randomized, double-blind, two-period, crossover study, healthy subjects were given either placebo or aspirin 1 gram three times daily for a total treatment period of 5 days. On Day 4 of each study period, a single 1 mg dose of glimepiride was administered. The glimepiride doses were separated by a 14-day washout period. Coadministration of aspirin and glimepiride resulted in a 34% decrease in the mean glimepiride AUC and a 4% decrease in the mean glimepiride C_{max} .

Colesevelam: Concomitant administration of colesevelam and glimepiride resulted in reductions in glimepiride $AUC_{0-\infty}$ and C_{max} of 18% and 8%, respectively. When glimepiride was administered 4 hours prior to colesevelam, there was no significant change in glimepiride $AUC_{0-\infty}$ or C_{max} , -6% and 3%, respectively [see *Dosage and Administration (2.1)* and *Drug Interactions (7.4)*].

Cimetidine and ranitidine: In a randomized, open-label, 3-way crossover study, healthy subjects received either a single 4 mg dose of glimepiride alone, glimepiride with ranitidine (150 mg twice daily for 4 days; glimepiride was administered on Day 3), or glimepiride with cimetidine (800 mg daily for 4 days; glimepiride was administered on Day 3). Co-administration of cimetidine or ranitidine with a single 4 mg oral dose of glimepiride did not significantly alter the absorption and disposition of glimepiride.

Propranolol: In a randomized, double-blind, two-period, crossover study, healthy subjects were given either placebo or propranolol 40 mg three times daily for a total treatment period of 5 days. On Day 4 of each study period, a single 2 mg dose of glimepiride was administered. The glimepiride doses were separated by a 14-day washout period. Concomitant administration of propranolol and glimepiride significantly increased glimepiride C_{max} , AUC, and $T_{1/2}$ by 23%, 22%, and 15%, respectively, and decreased glimepiride CL/f by 18%. The recovery of M1 and M2 from urine was not changed.

Warfarin: In an open-label, two-way, crossover study, healthy subjects received 4 mg of glimepiride daily for 10 days. Single 25 mg doses of warfarin were administered 6 days before starting glimepiride and on Day 4 of glimepiride administration. The concomitant administration of glimepiride did not alter the pharmacokinetics of R- and S-

warfarin enantiomers. No changes were observed in warfarin plasma protein binding. Glimepiride resulted in a statistically significant decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and maximum PT values during glimepiride treatment were 3.3% and 9.9%, respectively, and are unlikely to be clinically relevant.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies in rats at doses of up to 5000 parts per million (ppm) in complete feed (approximately 340 times the maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation that was dose-related and was thought to be the result of chronic pancreatic stimulation.

No adenoma formation in mice was observed at a dose of 320 ppm in complete feed, or 46 to 54 mg/kg body weight/day. This is at least 28 times the maximum human recommended dose of 8 mg once daily based on surface area.

Glimepiride was non-mutagenic in a battery of **in vitro** and *in vivo* mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, and mouse micronucleus test).

There was no effect of glimepiride on male mouse fertility in animals exposed up to 2500 mg/kg body weight (>1,500 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area).

14 CLINICAL STUDIES

14.1 Monotherapy

A total of 304 patients with type 2 diabetes already treated with sulfonylurea therapy participated in a 14-week, multicenter, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of glimepiride monotherapy. Patients discontinued their sulfonylurea therapy then entered a 3-week placebo washout period followed by randomization into 1 of 4 treatment groups: placebo (n=74), glimepiride 1 mg (n=78), glimepiride 4 mg (n=76) and glimepiride 8 mg (n=76). All patients randomized to glimepiride started 1 mg daily. Patients randomized to glimepiride 4 mg or 8 mg had blinded, forced titration of the glimepiride dose at weekly intervals, first to 4 mg and then to 8 mg, as long as the dose was tolerated, until the randomized dose was reached. Patients randomized to the 4 mg dose reached the assigned dose at Week 2. Patients randomized to the 8 mg dose reached the assigned dose at Week 3. Once the randomized dose level was reached, patients were to be maintained at that dose until Week 14. Approximately 66% of the placebo-treated patients completed the trial compared to 81% of patients treated with glimepiride 1 mg and 92% of patients treated with glimepiride 4 mg or 8 mg. Compared to placebo, treatment with glimepiride 1 mg, 4 mg and 8 mg daily provided statistically significant improvements in HbA1C compared to

placebo (Table 3).

Table 3: 14-week Monotherapy Trial Comparing Glimepiride to Placebo in Patients Previously Treated With Sulfonylurea Therapy ^a

	Placebo (N=74)	Glimepiride		
		1 mg (N=78)	4 mg (N=76)	8 mg (N=76)
HbA 1C (%)				
Baseline (mean)	n=59 8.0	n=65 7.9	n=65 7.9	n=68 8.0
Change from Baseline (adjusted mean ^b)	1.5	0.3	-0.3	-0.4
Difference from Placebo (adjusted mean ^b)		-1.2* (-1.5, -0.8)	-1.8* (-2.1, -1.4)	-1.8* (-2.2, -1.5)
Mean Baseline Weight				
Baseline (mean)	n=67 85.7	n=76 84.3	n=75 86.1	n=73 85.5
Change from Baseline (adjusted mean ^b)	-2.3	-0.2	0.5	1.0
Difference from Placebo (adjusted mean ^b)		2.0* (1.4, 2.7)	2.8* (2.1, 3.5)	3.2* (2.5, 4.0)

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

*p ≤0.001

A total of 249 patients who were treatment-naïve or who had received limited treatment with antidiabetic therapy in the past were randomized to receive 22 weeks of treatment with either glimepiride (n=123) or placebo (n=126) in a multicenter, randomized, double-blind, placebo-controlled, dose-titration trial. The starting dose of glimepiride was 1 mg daily and was titrated upward or downward at 2-week intervals to a goal FPG of 90 to 150 mg/dL. Blood glucose levels for both FPG and PPG were analyzed in the laboratory. Following 10 weeks of dose adjustment, patients were maintained at their optimal dose (1, 2, 3, 4, 6 or 8 mg) for the remaining 12 weeks of the trial. Treatment with glimepiride provided statistically significant improvements in HbA1C and FPG compared to placebo (Table 4).

Table 4: 22-Week Monotherapy Trial Comparing Glimepiride to Placebo in Patients Who Were Treatment-Naïve or Who Had No Recent Treatment with Antidiabetic Therapy ^a

	Placebo (N=126) Glimepiride (N=123)	
	n=97	n=106
HbA 1C (%)		
Baseline (mean)	9.1	9.3
Change from Baseline (adjusted mean ^b)	-1.1*	-2.2*
Difference from Placebo (adjusted mean ^b)	-1.1*	
95% confidence interval	(-1.5, -0.8)	
Body Weight (kg)		
Baseline (mean)	86.5	87.1
Change from Baseline (adjusted mean ^b)	-0.9	1.8
Difference from Placebo (adjusted mean ^b)	2.7	
95% confidence interval	(1.9, 3.6)	

^aIntent to treat population using last observation on study

^b Least squares mean adjusted for baseline value

* p ≤0.0001

16 HOW SUPPLIED/STORAGE AND HANDLING

Glimepiride tablets, USP are available in the following strengths and package sizes:

- 4 mg tablets (blue coloured, oval shaped, biconvex, uncoated tablets debossed with 'AHI 4' on one side and break line on the other) in bottles of 30 (NDC 51655-120-52) and 90 (NDC 51655-120-26)

Store at 25°C (77°F); excursions permitted to 20°C to 25°C (68°F to 77°F) (see USP Controlled Room Temperature).

Dispense in well-closed containers with safety closures.

17 PATIENT COUNSELING INFORMATION

Hypoglycemia

Explain the symptoms and treatment of hypoglycemia as well as conditions that predispose to hypoglycemia. Inform patients that their ability to concentrate and react may be impaired as a result of hypoglycemia and that this may present a risk in situations where these abilities are especially important, such as driving or operating other machinery [see *Warnings and Precautions (5.1)*].

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions may occur with glimepiride and that if a

reaction occurs to seek medical treatment and discontinue glimepiride [see *Warnings and Precautions (5.2)*].

Pregnancy

Advise females of reproductive potential to inform their prescriber of a known or suspected pregnancy [see *Use in Specific Populations (8.1)*].

Lactation

Advise breastfeeding women taking glimepiride to monitor breastfed infants for signs of hypoglycemia (e.g., jitters, cyanosis, apnea, hypothermia, excessive sleepiness, poor feeding, seizures) [see *Use in Specific Populations (8.2)*].

Manufactured For:

Accord Healthcare, Inc.,
1009 Slater Road,
Suite 210-B,
Durham, NC 27703,
USA.

Manufactured By:

Intas Pharmaceuticals Limited,
Ahmedabad -380 054, India.

10 1677 2 693003

Issued February 2019

Principal Display Panel

NDC: 51655-120-26



GLIMEPIRIDE

glimepiride tablet

Product Information

Product Type

HUMAN PRESCRIPTION
DRUG

Item Code (Source)

NDC:51655-120(NDC:16729-
003)

Route of Administration ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GLIMEPIRIDE (UNII: 6KY687524K) (GLIMEPIRIDE - UNII:6KY687524K)	GLIMEPIRIDE	4 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
POVIDONE (UNII: FZ989GH94E)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	

Product Characteristics

Color	blue	Score	2 pieces
Shape	OVAL	Size	11mm
Flavor		Imprint Code	AH1;4
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51655-120-52	30 in 1 BOTTLE, DISPENSING; Type 0: Not a Combination Product	12/29/2014	
2	NDC:51655-120-26	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	12/06/2022	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078181	12/29/2014	

Labeler - Northwind Pharmaceuticals, LLC (036986393)

Registrant - Northwind Pharmaceuticals, LLC (036986393)

Establishment

Name	Address	ID/FEI	Business Operations
Northwind Pharmaceuticals, LLC		036986393	repack(51655-120)

