INDICATIONS AND USAGE
AMARYL is a sulfonylurea indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. [see Clinical Studies (14.1)].

AMARYL should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. [see Warnings and Precautions (5.2)].

DOSE AND ADMINISTRATION
Recommended starting dose is 1 mg or 2 mg once daily. Increase in 1 or 2 mg increments no more frequently than every 1–2 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. Promptly discontinue AMARYL, assess for other causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes (5.2).

ADVERSE REACTIONS
Common adverse reactions in clinical trials (≥5% and more common than with placebo) include hypoglycemia, headache, nausea, and dizziness (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-333-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
Certain medications may affect glucose metabolism, requiring AMARYL dose adjustment and close monitoring of blood glucose (7.1).

Cytochrome P450 2C9 interactions: Inhibitors and inducers of cytochrome P450 2C9 may affect glycemic control by altering glimepiride plasma concentrations (7.3).

Coleselvam: Coadministration may reduce glimepiride absorption. AMARYL should be administered at least 4 hours prior to coleselvam (7.1, 7.4).

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

OVERDOSAGE

In general, treatment involves management of glucose levels and support of vital functions. There is no specific antidote for AMARYL.

Patients being transferred to AMARYL from longer half-life sulfonylureas (e.g., chlorpropamide) may have overlapping drug effect for 1–2 weeks and should be appropriately monitored for hypoglycemia. When coleselvam is coadministered with glimepiride, maximum plasma concentration and total exposure to glimepiride is reduced. Therefore, AMARYL should be administered at least 4 hours prior to coleselvam.

1.1 Important Limitations of Use

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

The recommended starting dose of AMARYL 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 Dose and Administration (2.1)].

Patients being transferred to AMARYL from longer half-life sulfonylureas (e.g., chlorpropamide) may have overlapping drug effect for 1–2 weeks and should be appropriately monitored for hypoglycemia. When coleselvam is coadministered with glimepiride, maximum plasma concentration and total exposure to glimepiride is reduced. Therefore, AMARYL should be administered at least 4 hours prior to coleselvam.

1.1 Important Limitations of Use

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

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2.1 Recommended Dosing

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

The recommended starting dose of AMARYL 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 Dose and Administration (2.1)].

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. Up titration should not occur more frequently than every 1–2 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.

3. DOSAGE FORMS AND STRENGTHS

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

4. CONTRAINDICATIONS

AMARYL 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 AMARYL. Do not use AMARYL in patients who have a history of an allergic reaction to sulfonamide derivatives.

FULL PRESCRIBING INFORMATION CONTENTS
1 INDICATIONS AND Usage
1. Important Limitations of Use
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 Macravascular Outcomes
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Drugs Affecting Glucose Metabolism
7.2 Miconazole
7.3 Cytochrome P450 2C9 Interactions
7.4 Concomitant Administration of Colesevelam
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL 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
17.1 Information for Patients

*Sections or subsections omitted from the full prescribing information are not listed.
Reported hypersensitivity reactions include cutaneous eruptions with or without pruritus as well as more serious reactions (e.g., anaphylaxis, angioedema, Stevens-Johnson syndrome, dyspnea) [see Warnings and Precautions (5.2) and Adverse Reactions (6.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypoglycemia

Insufficient information to determine whether any of the accidental injury events were associated with and consider the use of a non-sulfonylurea alternative. There are also postmarketing reports of (G6PD) deficiency. Because AMARYL is a sulfonylurea, use caution in patients with G6PD deficiency for the reaction, and institute alternative treatment for diabetes.

5.2 Hypersensitivity Reactions

Hypoglycemia in patients who received placebo. All of these events were self-treated.

In a randomized, double-blind, placebo-controlled monotherapy trial of 14 weeks duration, patients already on sulfonylurea therapy underwent a 3-week washout period then were randomized to AMARYL mg, 4 mg, 8 mg or placebo. Patients randomized to AMARYL 4 mg or 8 mg underwent forced-hydration from an initial dose of 1 mg to these final doses, as tolerated [see Clinical Studies (14.1)]. The overall incidence of possible hypoglycemia (defined by the presence of at least one symptom that the investigator believed might be related to hypoglycemia; a concurrent glucose measurement was not required) was 4% for AMARYL 1 mg, 17% for AMARYL 4 mg, 16% for AMARYL 8 mg and 0% for placebo. All of these events were self-treated.

In a randomized, double-blind, placebo-controlled monotherapy trial of 22 weeks duration, patients received a starting dose of either 1 mg AMARYL or placebo daily. The dose of AMARYL was titrated to a target fasting plasma glucose of 50–120 mg/dL. Final daily doses of AMARYL were 1, 2, 3, 4, 6 or 8 mg [see Clinical Studies (14.1)]. The overall incidence of possible hypoglycemia (as defined above for the 14-week trial) for AMARYL vs. placebo was 19.7% vs. 3.2%. All of these events were self-treated.

Weight gain: AMARYL, like all sulfonylureas, can cause weight gain [see Clinical Studies (14.1)]. Allergic Reactions: In clinical trials, allergic reactions, such as pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occurred in less than 1% of AMARYL-treated patients. These may resolve despite continued treatment with AMARYL. There are postmarketing reports of more serious allergic reactions (e.g., dyspnea, hypotension, shock) [see Warnings and Precautions (5.2), Laboratory Tests: Elevated Serum Alanine Aminotransferase (ALT)]. In 11 pooled placebo-controlled trials of AMARYL, 1.6% of AMARYL-treated patients and 0.8% of placebo-treated patients developed serum ALT greater than three times the upper limit of the reference range.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of AMARYL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

6.3 Macrocovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with AMARYL 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)]

In clinical trials, the most common adverse reactions with AMARYL were hypoglycemia, dizziness, asthenia, headache, and nausea.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Approximately 2,903 patients with type 2 diabetes have been treated with AMARYL in the controlled clinical trials. In these trials, approximately 1,700 patients were treated with AMARYL for at least 1 year.

Table 1 summarizes adverse events, other than hypoglycemia, that were reported in 11 pooled placebo-controlled trials, whether or not considered to be possibly or probably related to study medication. Treatment with AMARYL ranged from 13 weeks to 12 months. Terms that are reported represent those that occurred at an incidence of ≥5% among AMARYL-treated patients and more commonly than in patients who received placebo.

Table 1. Eleven Pooled Placebo-Controlled Trials ranging from 13 weeks to 12 months: Adverse Events (Excluding Hypoglycemia) Occurring in ≥5% of AMARYL-treated Patients and at a Greater Incidence than with Placebo

<table>
<thead>
<tr>
<th></th>
<th>AMARYL N=745</th>
<th>Placebo N=294</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Events</strong></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Headache</td>
<td>8.2</td>
<td>7.8</td>
</tr>
<tr>
<td>Accidental Injury†</td>
<td>5.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Flu Syndrome</td>
<td>5.4</td>
<td>4.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>5.0</td>
<td>3.4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5.0</td>
<td>2.4</td>
</tr>
</tbody>
</table>

*AMARYL doses ranged from 1–16 mg administered daily
†Insufficient information to determine whether any of the accidental injury events were associated with hypoglycemia

Hypoglycemia:

In a randomized, double-blind, placebo-controlled monotherapy trial of 14 weeks duration, patients already on sulfonylurea therapy underwent a 3-week washout period then were randomized to AMARYL mg, 4 mg, 8 mg or placebo. Patients randomized to AMARYL 4 mg or 8 mg underwent forced-hydration from an initial dose of 1 mg to these final doses, as tolerated [see Clinical Studies (14.1)]. The overall incidence of possible hypoglycemia (defined by the presence of at least one symptom that the investigator believed might be related to hypoglycemia; a concurrent glucose measurement was not required) was 4% for AMARYL 1 mg, 17% for AMARYL 4 mg, 16% for AMARYL 8 mg and 0% for placebo. All of these events were self-treated.

In a randomized, double-blind, placebo-controlled monotherapy trial of 22 weeks duration, patients received a starting dose of either 1 mg AMARYL or placebo daily. The dose of AMARYL was titrated to a target fasting plasma glucose of 50–120 mg/dL. Final daily doses of AMARYL were 1, 2, 3, 4, 6 or 8 mg [see Clinical Studies (14.1)]. The overall incidence of possible hypoglycemia (as defined above for the 14-week trial) for AMARYL vs. placebo was 19.7% vs. 3.2%. All of these events were self-treated.

Weight gain: AMARYL, like all sulfonylureas, can cause weight gain [see Clinical Studies (14.1)].

6.1 CONCURRENT ADMINISTRATION OF COLESEVelem

Colesevelam can reduce the maximum plasma concentration and total exposure of glipizide when the two are coadministered. However, absorption is not reduced when glipizide is administered 4 hours prior to colesevelam. Therefore, AMARYL should be administered at least 4 hours prior to colesevelam.
Hypoglycemic events documented by blood glucose values <36 mg/dL were observed in 4% of pediatric patients treated with AMARYL, and in 1% of pediatric patients treated with metformin. One patient in each treatment group experienced a severe hypoglycemic episode (severely was determined by the investigator based on observed signs and symptoms).

8.5 Geriatric Use
In clinical trials of AMARYL, 1053 of 3491 patients (30%) were >65 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

There were no significant differences in glimepiride pharmacokinetics between patients with type 2 diabetes and those >65 years (n=49) [see Clinical Pharmacology (12.3)]. Glimepiride is substantially excreted by the kidney. Elderly patients are more likely to have renal impairment. In addition, hypoglycemia may be difficult to recognize in the elderly [see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]. Use caution when initiating AMARYL and increasing the dose of AMARYL in this patient population.

8.6 Renal Impairment
To minimize the risk of hypoglycemia, the recommended starting dose of AMARYL is 1 mg daily for all patients with type 2 diabetes and renal impairment [see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]. A multiple-dose titration study was conducted in 16 patients with type 2 diabetes and renal impairment using doses ranging from 1 mg to 8 mg daily for 3 months. Baseline creatinine clearance ranged from 10-60 mL/min. The pharmacokinetics of AMARYL were evaluated in the multiple-dose titration study and the results were consistent with those observed in patients enrolled in a single-dose study. In both studies, the relative total clearance of AMARYL increased when kidney function was impaired. Both studies also demonstrated that the elimination of the two major metabolites was reduced in patients with renal impairment [see Clinical Pharmacology (12.3)].

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 2-3 hours after single oral doses of AMARYL. The effects of AMARYL on HbA1c, fasting plasma glucose, and post-prandial glucose have been assessed in clinical trials [see Clinical Studies (14.1)].

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 (Cmax) 2 to 3 hours post-dose. When glimepiride was given with meals, the mean Cmax and AUC (area under the curve) were decreased by 6% 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 intra- and inter-individual variabilities of glimepiride pharmacokinetic parameters were 15-23% and 24-29%, 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 ingestion of food. 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 cytoxic enzymes. M2 is inactive. In animals, M1 poses as one of the pharmacologically active metabolites of glimepiride, but it is unclear whether M1 results in clinically meaningful effects on blood glucose in humans. Excretion: When "C-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%-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 bilateral distribution of glimepiride or its M1 metabolite was observed.

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 AMARYL 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the two age groups. The mean

3
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 differences have been conducted to assess the effects of race on glimepiride pharmacokinetics but in placebo-controlled trials of AMARYL 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: A single-dose, open-label study AMARYL 3 mg was administered to patients with mild, moderate, and severe renal impairment as estimated by creatinine clearance (ClCr). Group I consisted of 5 patients with mild renal impairment (ClCr > 50 mL/min). Group II consisted of 3 patients with moderate renal impairment (ClCr = 20–50 mL/min) and Group III consisted of 7 patients with severe renal impairment (ClCr < 20 mL/min). Although, glimepiride serum concentrations decreased with decreasing renal function, Group III had a 2.3-fold higher mean AUC for M2 and an 8.6-fold higher mean AUC for M2 compared to corresponding mean AUC in Group I. The apparent terminal half-life (T1/2) 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 21.7% for Group III.

Hepatic Impairment: It is unknown whether there is an effect of hepatic impairment on AMARYL pharmacokinetics because the pharmacokinetics of AMARYL 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 mean 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 Cmax and AUC than those of normal weight. The mean Cmax, AUC<sub>0-∞</sub>, and AUC<sub>0-24</sub> values of glimepiride in normal volunteers and obese patients were 574 ± 218 ng/mL, 410 ± 124 ng/mL, 2130 ± 1036 hours ng/mL vs. 2820 ± 1110 hours ng/mL and 4000 ± 1230 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 AMARYL was administered. The AMARYL doses were separated by a 14-day washout period. Co-administration of aspirin and AMARYL resulted in a 34% decrease in the mean glimepiride C<sub>max</sub> and a 4% decrease in the mean glimepiride C<sub>τ</sub>.

Colestyramine: Concomitant administration of colestevam and glimepiride resulted in reductions in glimepiride C<sub>τ</sub>, AUC<sub>0-≤</sub>, and C<sub>max</sub> of 18% and 8%, respectively. When glimepiride was administered 4 hours prior to colestevam, there was no significant change in glimepiride AUC<sub>0-≤</sub> or C<sub>τ</sub> at 6% and 3%, respectively (see Drug Interactions (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 AMARYL alone, AMARYL with ranitidine (150 mg daily for 4 days; AMARYL was administered on Day 3), or AMARYL with cimetidine (800 mg daily for 4 days; AMARYL was administered on Day 4). Co-administration of ranitidine and glimepiride with a single 4 mg oral dose of AMARYL 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 or each study period, a single 2 mg dose of AMARYL was administered. The AMARYL doses were separated by a 14-day washout period. Concomitant administration of propranolol and AMARYL significantly increased glimepiride C<sub>τ</sub>, AUC, and C<sub>max</sub> by 23%, 22%, and 15%, respectively, and decreased glimepiride Clτ 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 AMARYL daily for 10 days. Glimepiride doses of warfarin were administered 6 days before warfarin was discontinued and 4 days after the last dose of AMARYL on Day 4 of AMARYL administration. The concomitant administration of AMARYL did not alter the pharmacokinetics of R- and S-warfarin enantiomers. No changes were observed in warfarin plasma protein binding. AMARYL resulted in a statistically significant decrease in the pharmacodynamic response to warfarin.

The AUC in the mean area under the prothrombin time (PT) curve and maximum PT values of glimepiride during AMARYL 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 5 to 5000 parts per million (ppm) in complete feed (approximately 4,000 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 340 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 AMARYL 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), AMARYL 1 mg (n=76), AMARYL 4 mg (n=76) and AMARYL 8 mg (n=76). All patients randomized to AMARYL started 1 mg daily. Patients randomized to AMARYL 4 mg or 8 mg had blinded, forced titration of the AMARYL 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 86% 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 AMARYL 1 mg, 4 mg and 8 mg daily provided statistically significant improvements in HbA1C compared to placebo (Table 3).
17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients
Inform patients about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose.
Inform patients about the potential side effects of AMARYL including hypoglycemia and weight gain.
Explain the symptoms and treatment of hypoglycemia as well as conditions that predispose to hypoglycemia. Patients should be informed that the ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.
Patients with diabetes should be advised to inform their healthcare provider if they are pregnant, contemplating pregnancy, breastfeeding, or contemplating breastfeeding.

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