DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Kimberly Davis
US Drug Regulatory Affairs, Marketed Products
Aventis Pharmaceuticals Inc.
399 Interpace Parkway
Mailstop: PNJ4-M1364
Parsippany, NJ 07054

RE: Amaryl® (glimepiride) Tablets
NDA 20-496
MACMIS ID#9731

Dear Ms. Davis:

This letter concerns several promotional materials (sales aids 50059159/20144201/3443R0 and 50059158/20142501/3337R06, brochure 20058305/2196M0, and web site www.amaryl.com) for Amaryl tablets (glimepiride) disseminated by Aventis Pharmaceuticals Inc. (Aventis). As part of its monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed these materials and has concluded that they are false or misleading, in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Our specific objections follow.

Misleading Mechanism of Action Presentation

According to the PI, "The **primary** mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extrapancreatic effects may also play a role in the activity of sulfonylureas such as glimepiride." However, your materials (sales aids 50059159/20144201/3443R0 and 50059158/20142501/3337R06 and web site) prominently display headlines such as "Amaryl is tailored to improve insulin sensitivity," "Amaryl is tailored to demonstrate an insulin-sensitizing effect," and "Tailored glucose control with Amaryl means…Improving insulin sensitivity and targeting insulin resistance." These claims and related presentations are misleading because they strongly suggest that Amaryl works primarily by improving insulin sensitivity and targeting insulin resistance when such is not the case.

Misleading Efficacy Claims

Promotional materials are misleading if they suggest that a drug is more effective than has been demonstrated by substantial evidence. Your sales aids (50059159/20144201/3443R0 and 50059158/20142501/3337R06) prominently present efficacy claims that are unsubstantiated and inconsistent with the approved product labeling (PI). For example, you present claims that Amaryl decreased HbA1c by 2.4% and 3.7% in patients with baseline HbA1c of 9.1 and 11.3, respectively.

The claim supposedly demonstrating the 3.7% decrease in HbA1c is based on a study that involved a total of 30 patients with baseline HbA1c of 11.3. In contrast, the PI indicates that the average net reduction in HbA1c with Amaryl in 720 patients treated with 8 mg once daily was 2.0% compared with placebo treated patients. Therefore, your presentations are misleading because they suggest that Amaryl is more effective than has been demonstrated by substantial evidence.

Your brochure (20058305/2196M0) and web site include claims that "84% [of patients on Amaryl] with mean baseline HbA1c of 9.1% achieved HbA1c < 8.0%," "82% of these patients achieved HbA1c ≤7.2%," and "Amaryl achieves tight HbA1c control (HbA1c ≤7.2%)...." However, your claim that 82% of patients had "tight glycemic control" as defined by HbA1c <7.2% is misleading because only 69% of patients treated with Amaryl had this level of response according to the study offered in support of the claim. Moreover, you fail to disclose that 32% of placebo treated patients also achieved this level of response.

Requested Action

Aventis should immediately discontinue these and all other promotional materials for Amaryl that contain the same or similar claims or presentations. We request that Aventis respond, in writing, with its intent to comply with the above. DDMAC should receive your written response no later than March 22, 2001. This response should list all similarly violative materials with a description of the method for discontinuation and the discontinuation date.

If you have any questions or comments, please contact me by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #9731 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Barbara S. Chong, Pharm.D., BCPS
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

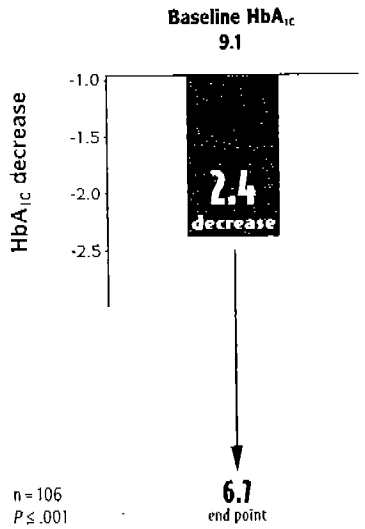
/s/

Barbara Chong
3/8/01 09:12:54 AM

Tailored Glucose Control with Amaryl means...

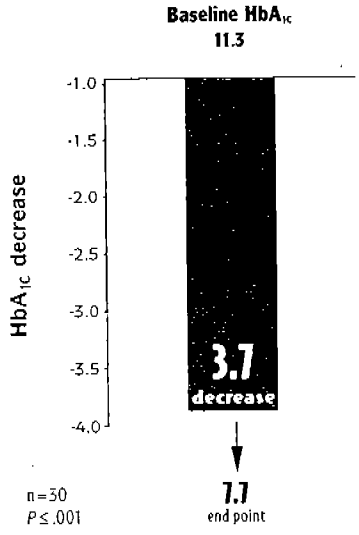
AMARYL IS TAILORED TO SAFELY DELIVER TIGHT CONTROL

Tight control achieved ($HbA_{1c} \leq 7.2\%$)[7*]



Values are presented as median.
Source: Schade et al[7]
Tight control is defined by the UKPDS as $HbA_{1c} < 7.0\%$[14]

Significant HbA_{1c} reduction even in patients with high baseline HbA_{1c} (10.5-14.3)[1]



Values are presented as median.
Source: Data on file[1]

Safe for Patients With Renal Impairment (CLcr = 9.4 mL/min)[1]

- **60% renal, 40% hepatic dual route of elimination—100% biotransformed**
- Because renally impaired patients may be more sensitive to the glucose-lowering effect of Amaryl, begin with 1 mg daily and titrate based on fasting blood glucose levels

Favorable Safety Profile

- **0.9% to 1.7% incidence of hypoglycemia** as documented by blood glucose <60 mg/dL[1]
- Neutral effect on plasma lipids (HDL, LDL, and triglycerides)
- Other most common adverse reactions (≥1%) (n = 746) include dizziness (1.7%), asthenia (1.6%), headache (1.5%), and nausea (1.1%)

The controversial UGDP trial found that use of hypoglycemic agents was associated with an increased risk of cardiovascular complications.

Fasting blood glucose and HbA_{1c} measurements should be performed to monitor patient response to therapy and to determine the minimum effective dose for each patient.

*Multicenter, placebo-controlled study of 247 patients who failed on diet and exercise.

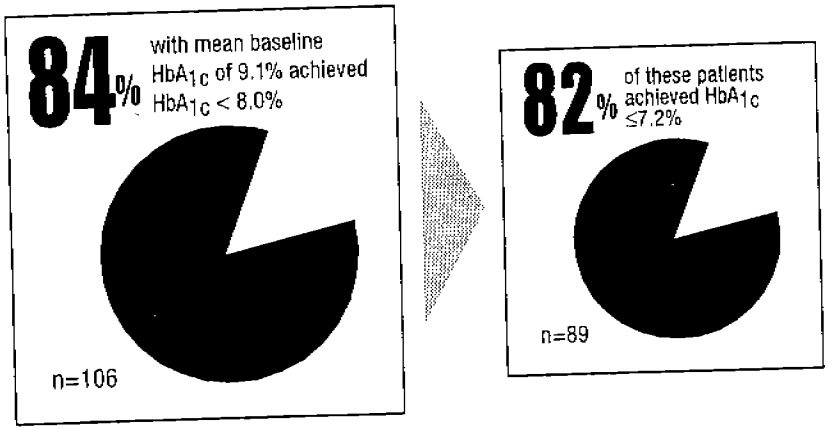
During our last meeting,
Dr. Jones,
you asked about the efficacy of Amaryl.
As the results of this study suggest,
Amaryl delivers highly effective glucose control.

Study Design

- Multicenter U.S. study in 247 patients who failed on diet and exercise

Efficacy Results

Amaryl achieves tight HbA_{1c} control ($HbA_{1c} \leq 7.2\%$) as defined by the DCCT in patients with mean baseline HbA_{1c} of 9.1%[1,3,4]



- 60% of patients with mean baseline HbA_{1c} >10% also achieved tight control ($HbA_{1c} \leq 7.2\%$)
- 2% median HbA_{1c} reduction in Amaryl patients ($P < 0.001$)
- Amaryl reduced HbA_{1c} from HbA_{1c} >9% to <7%, resulting in a median HbA_{1c} of 8.7% — a 1.4% greater reduction than placebo ($P < 0.001$)

ONCE-A-DAY
Amaryl®
glimepiride TABLETS

Aventis

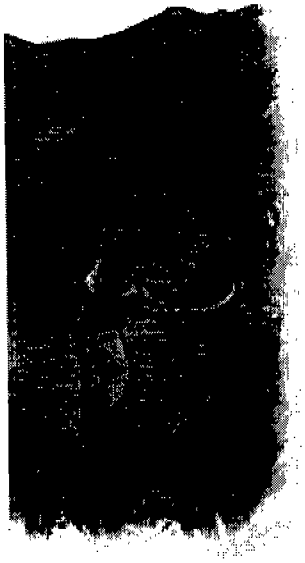
ONCE-A-DAY
Amaryl®
glimepiride TABLETS
Tailored Glucose Control
For Type 2 Diabetes

Navigate Amaryl.com

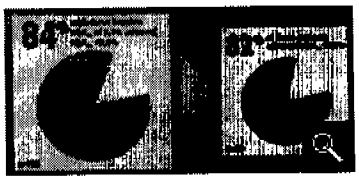
This site is intended for U.S. health care professionals only.

Amaryl At A Glance

Prescribing Information



Amaryl Delivers Highly Effective Tailored Glucose Control



Provides tight control ($HbA_{1c} \leq 7.2\%$) as defined by the DCCT in patients with mean baseline HbA_{1c} of 9.1%[1,7,14]*

- 60% of patients with mean baseline HbA_{1c} >10% also achieved tight control ($HbA_{1c} \leq 7.2\%$)

Amaryl Maintains Proven Long-Term Control

With QD Dosing

- In a 1-year study, once-daily dose of **Amaryl** achieved glycemic control comparable to once- or twice-daily dose of glyburide (n = 1044)[5]

In Conditions Of Everyday Life

- In 2 long-term studies (n = 1892), **Amaryl** patients maintained control for periods of up to 2.5 years under conditions of everyday life

The effectiveness of all oral hypoglycemic agents, including **Amaryl**, tends to decrease over time.

*Multicenter, placebo-controlled study of 247 patients who failed on diet and exercise.

Tailored benefits to meet your patients' needs.

Professional Home | Amaryl At A Glance | Product Information
Clinical Management | Professional Resources
Aventis Pharmaceuticals U.S. Home | Prescribing Information

Patient Home