DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**TRANSMITTED BY FACSIMILE**

Barry Reit, Ph.D.
Vice President, Regulatory Affairs
Novo Nordisk Pharmaceuticals, Inc.
100 College Road West
Princeton, NJ 08540

**RE: Prandin™ (repaglinide) Tablets**
NDA 20-741
MACMIS ID#9997

Dear Mr. Reit:

This letter concerns several promotional materials (sales aid 124518; professional exhibit panels 124597; and posters 124421A, 124421C, 124421E) for Prandin (repaglinide) disseminated by Novo Nordisk Pharmaceuticals, Inc. (NNPI). As part of its monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed these promotional materials and has concluded that they are false or misleading, in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Our specific objections follow.

**Minimizing Risk of Hypoglycemia**

In sales aid 124518, poster 124421E, and exhibit panels 124597, you present statements such as "Prandin offers unique safety advantages," "Low risk of severe hypoglycemia," and "Lower risk of hypoglycemia vs glyburide, even when a meal is missed" along with a graphic that patients treated with Prandin experienced a 0% incidence of hypoglycemic events in a skip-a-meal study. However, according to the Adverse Reactions section of the approved product labeling (PI), hypoglycemia occurred in 31% of Prandin-treated patients in placebo-controlled trials. This fact is not presented in your materials. The PI also states that in active controlled trials, "Mild or moderate hypoglycemia occurred in 16% of Prandin patients...." Moreover, the PI states that 13% of Prandin treated patients discontinued Prandin treatment due to adverse events over one year, and the most common adverse events leading to withdrawal were hyperglycemia, hypoglycemia, and related symptoms. Your disclosure that 16% of patients on Prandin experienced mild to moderate hypoglycemia on the bottom of poster 124421E and the exhibit panels, in extremely small type, fails to correct the misleading suggestion that Prandin is either not associated with hypoglycemia or has a low incidence of hypoglycemia. Your minimization of this known risk is particularly concerning since the potential risks associated with hypoglycemia raise significant safety concerns.

In sales aid 124518, you state "Neutral effect on weight: no clinically significant effect on weight in long-term clinical trials." This statement is misleading because it is inconsistent with the PI, which states, "The average weight gain in patients treated with Prandin and not previously treated with sulfonylurea drugs was 3.3%."

**Broadened Indication**

In sales aid 124518 and poster 124421A, you present statements such as "In type 2 diabetes beware PPG spike can threaten cardiovascular health," "In type 2 diabetes the added burden of high mealtime glucose loads: Cardiovascular risk," and "As postprandial glucose levels increase, so do cardiovascular risks." In addition, you present a graph depicting an increased incidence of mortality and myocardial infarction with increasing levels of postprandial glucose. According to your PI, "Prandin is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with type 2 diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled satisfactorily by diet and exercise alone. Prandin is also indicated for use in combination with metformin to lower blood glucose in patients whose hyperglycemia cannot be controlled by exercise, diet, and either repaglinide or metformin alone." Therefore, these presentations are misleading because they suggest that Prandin is indicated to reduce cardiovascular morbidity and mortality, when such has not been demonstrated by substantial evidence.

**Unsubstantiated Superiority Claims**

Promotional materials are misleading if they suggest that a drug is superior to other products when such has not been demonstrated by substantial evidence. In poster 124421E and sales aid 124518, you present prominent headers such as "Prandin offers unique safety advantages," "Choose Prandin instead of a sulfonylurea," and "The Prandin advantage" along with a comparison of the profile of Prandin and selected oral sulfonylureas. These presentations are misleading because they imply that Prandin is superior to the sulfonylureas, when such has not been demonstrated by substantial evidence.

**Requested Action**

NNPI should immediately discontinue these and all other promotional materials for Prandin that contain the same or similar claims or presentations. We request that NNPI respond, in writing, with its intent to comply with the above. DDMAC should receive your written response no later than May 15, 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 #9997 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

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

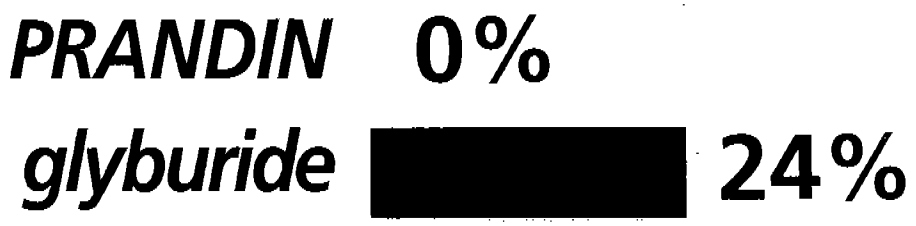
/s/

Barbara Chong
5/1/01 03:53:47 PM

# **PRANDIN** offers unique safety advantages

- Lower risk of hypoglycemia *vs* glyburide, even when a meal is missed[7*]

**Patients experiencing hypoglycemic events in a skip-a-meal study (%)**




Skip-a-meal study, 2-meal day.[7]

- Low risk of hyperinsulinemia: insulin levels return toward baseline between meals and during the night

*PRANDIN patients (n=18) were dosed with each meal (2 or 3 per day); glyburide patients (n=25) took 1 or 2 daily doses regardless of whether or not they skipped a meal.[7]

Please see full prescribing information in pocket.

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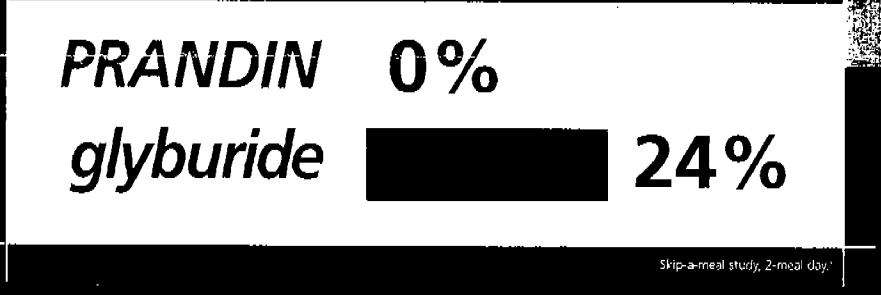
# Choose PRANDIN
## to Control PPG Spikes

### The PRANDIN advantage

- Acts rapidly to control postprandial glucose surges
- Reductions in PPG levels are significant *vs* placebo
- Postprandial effect complements the action of metformin in combination therapy
- Flexible mealtime dosing reduces risk of hypoglycemia when meals are missed
- Lower risk of hypoglycemia *vs* glyburide, even when a meal is missed[1*]

**Patients experiencing hypoglycemic events in a skip-a-meal study (%)**




Skip-a-meal study, 2-meal day.[1]

- Low risk of hyperinsulinemia: insulin levels return toward baseline between meals and during the night
- May be used in patients with renal insufficiency†

***Get Control of PPG Spikes***

**PRANDIN®**
**repaglinide TABLETS**

*An adjunct to diet and exercise*

In clinical trials, the most common adverse events leading to discontinuation of PRANDIN* therapy were hyperglycemia, hypoglycemia, and related symptoms. The most common other side effects reported were cold- and flu-like symptoms, headache, diarrhea, joint ache, and back pain.

Cardiovascular events also occur commonly in patients with type 2 diabetes. In one-year comparator trials, the incidence of individual events was not greater than 1% except for chest pain (1.8%) and angina (1.8%). The individual incidence of other cardiovascular events (hypertension, abnormal EKG, myocardial infarction, arrhythmias, and palpitations) was ≤ 1% and not different for PRANDIN* and the comparator drugs.

* PRANDIN patients (n=18) were dosed with each meal (2 or 3 per day); glyburide patients (n=25) took 1 or 2 daily doses regardless of whether or not they skipped a meal. In 1-year controlled trials comparing PRANDIN (n=1228) with sulfonylureas (n=498), for efficacy and safety, symptoms of mild to moderate hypoglycemia were reported in 16% of PRANDIN-treated patients; none developed coma or required hospitalization. Hypoglycemia was reported in 20% of patients treated with sulfonylureas (glyburide and glipizide).

† No initial dose adjustment required. Subsequent dosing increases should be made carefully.


**Reference:** 1. Damsbo P, Clausen P, Marbury TC, Windfeld K. A double-blind randomized comparison of meal-related glycemic control by repaglinide and glyburide in overweight type 2 diabetic patients. *Diabetes Care.* 1999;22:789-794.


Please see a representative for full prescribing information. PRANDIN is a registered trademark of Novo Nordisk A/S. © 2001 Novo Nordisk Pharmaceuticals, Inc. PRAN-48(SA-E 124597 March 2001

novo nordisk®

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# **PRANDIN** prescribed in over 500,000 patients with type 2 diabetes[8]

**Safety confirmed in clinical use**

- Neutral effect on weight: no clinically significant effect on weight in long-term clinical trials[3]
- Neutral effect on lipids: no significant changes in plasma lipids in long-term clinical trials[3]
- No requirement for LFT monitoring
- May be used in patients with renal insufficiency†

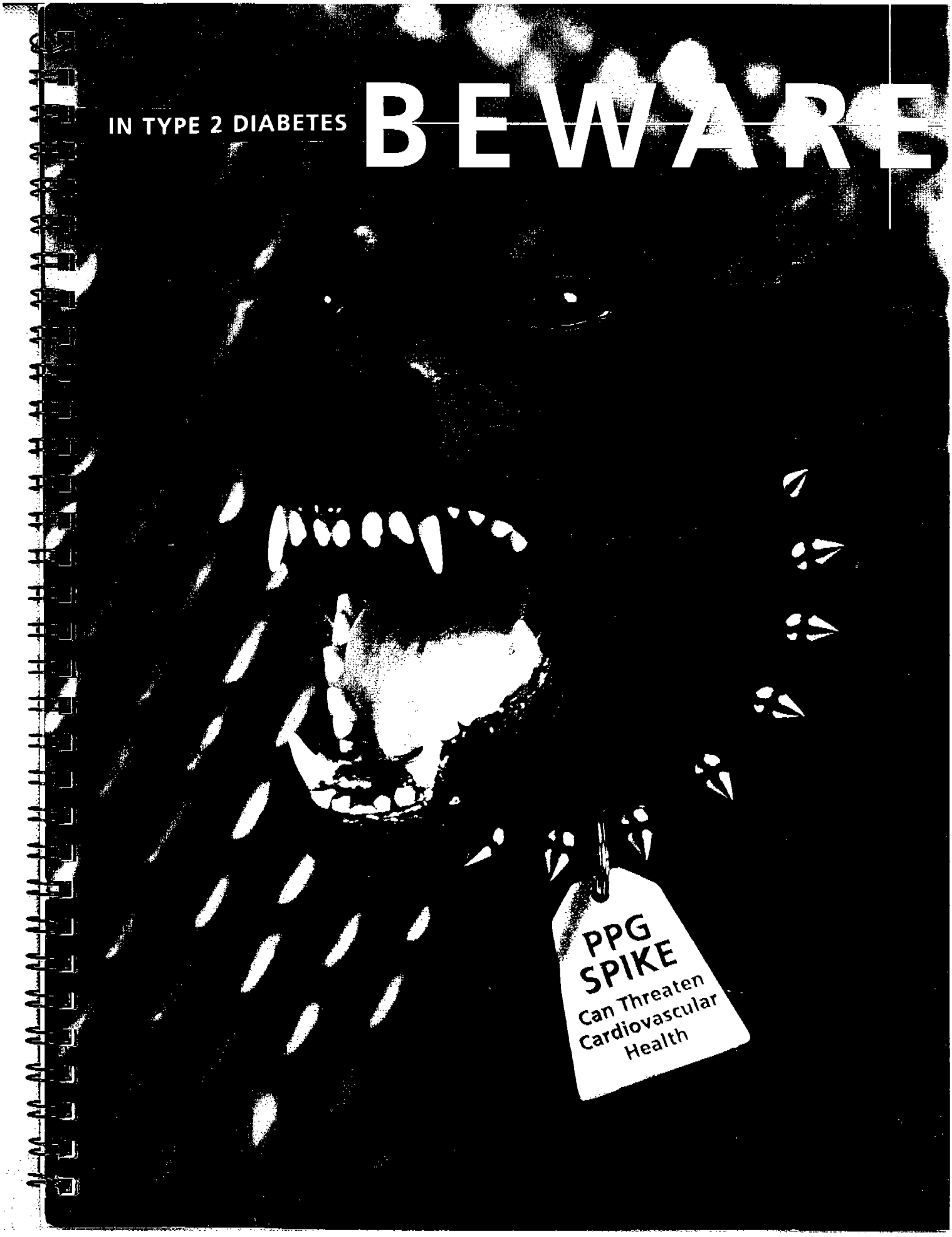
In 1-year controlled trials comparing PRANDIN (n=1228) with sulfonylureas (n=498) for efficacy and safety, symptoms of mild to moderate hypoglycemia were reported in 16% of PRANDIN-treated patients; none developed coma or required hospitalization. Hypoglycemia was reported in 20% of patients treated with sulfonylureas (glyburide and glipizide).

†No initial dose adjustment required. Subsequent dosing increases should be made carefully.

***Get Control of PPG Spikes***

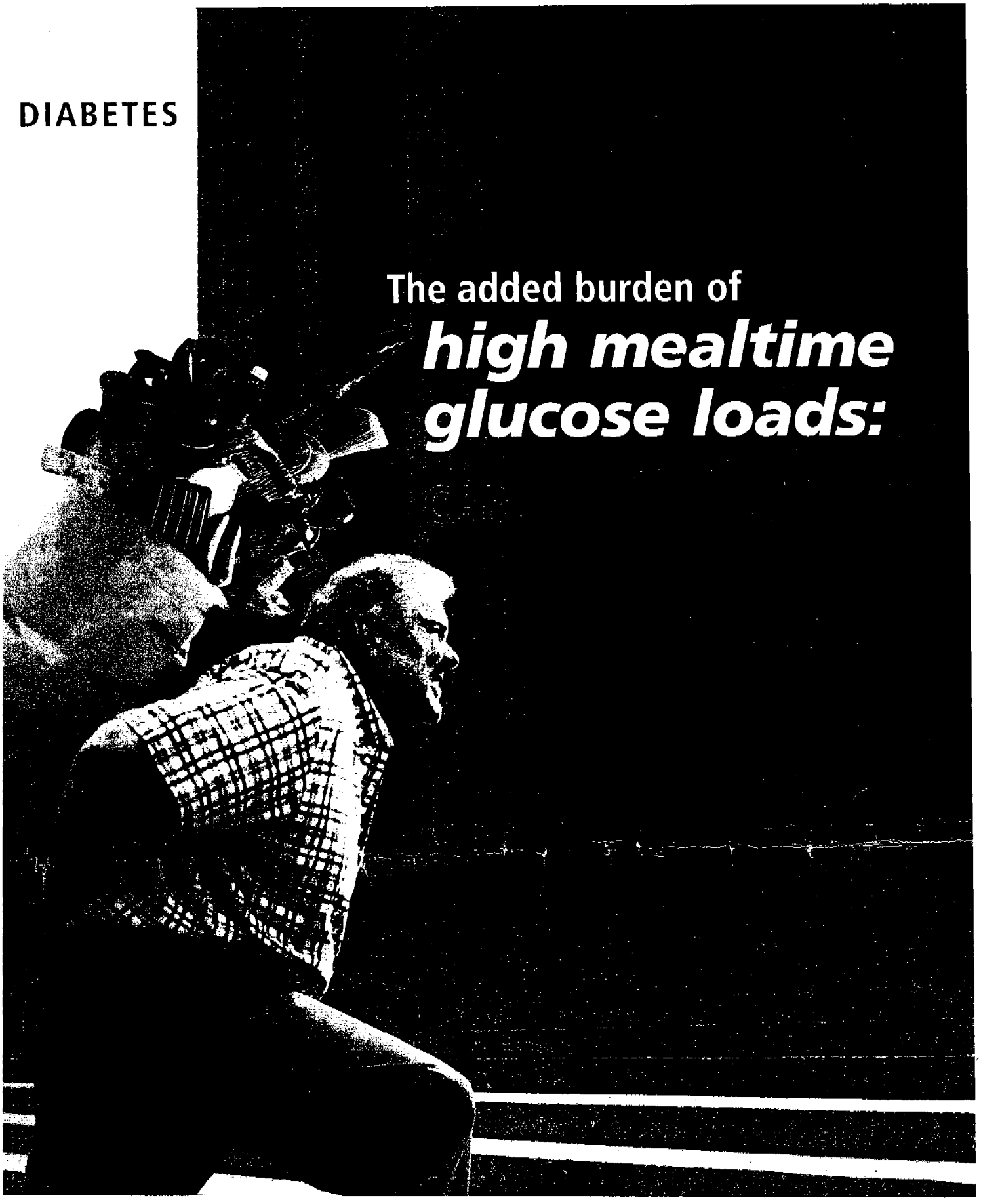
**PRANDIN®**
repaglinide TABLETS

*An adjunct to diet and exercise*


IN TYPE 2 DIABETES
BEWARE
PPG
SPIKE
Can Threaten
Cardiovascular
Health

DIABETES

# The added burden of *high mealtime glucose loads:*



# As postprandial glucose levels increase, so does **CARDIOVASCULAR RISK**

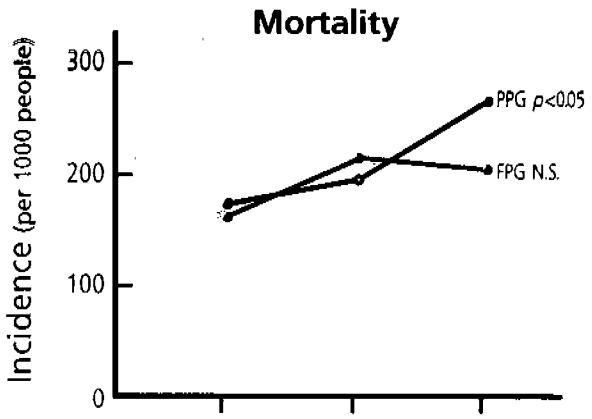
**Postprandial hyperglycemia may exist even with normal fasting plasma glucose**

In a study of over 25,000 people followed for up to 10 years, high postprandial plasma glucose (PPG) levels were associated with an increased risk of death, independently of fasting blood glucose.[1]

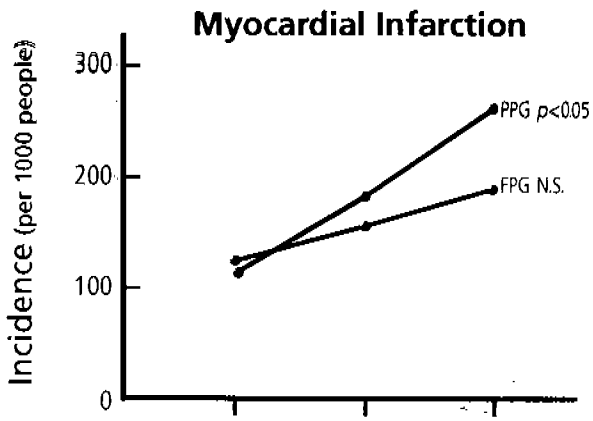
DECODE Study Group, *The Lancet*, 1999

## Incidence of Myocardial Infarction and Mortality

(rate per 1000 people classified by quality of glucose control)




| Level of Glucose Control: | Good | Borderline | Poor |
|---|---|---|---|
| FPG levels: (mg/dL) | 88-110 | ≤140 | >140 |
| PPG levels: (mg/dL) | 79-144 | ≤180 | >180 |




| Level of Glucose Control: | Good | Borderline | Poor |
|---|---|---|---|
| FPG levels: (mg/dL) | 88-110 | ≤140 | >140 |
| PPG levels: (mg/dL) | 79-144 | ≤180 | >180 |

Adapted from Hanefeld et al.[2]

# PRANDIN vs the sulfonylureas

**Profile of PRANDIN and selected oral sulfonylureas**

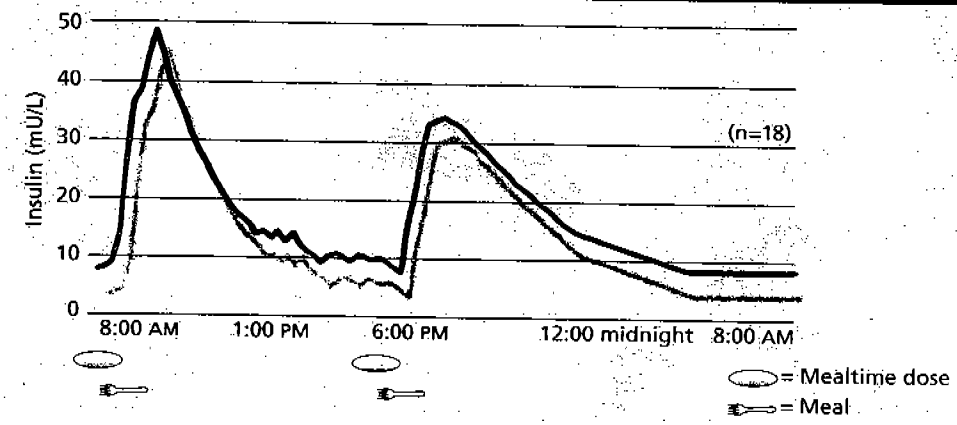
| | PRANDIN[1] | Glyburide[2] (micronized and regular) | Glipizide[3] (extended release) | Glimepiride[4] |
|---|---|---|---|---|
| Action | **Stimulates mealtime insulin release with mealtime dosing (each meal)** | Stimulates extended insulin release with once- or twice-daily dosing | Stimulates extended insulin release with once-daily dosing | Stimulates extended insulin release with once-daily dosing |
| Time to peak plasma levels ($T_{max}$) | **1.0 to 1.4 hours** | 2 to 4 hours | 6 to 12 hours | 2 to 3 hours |
| Duration of action | **Short (meal-associated)** | Medium to long | Long (extended release) | Long |
| Elimination half-life ($T_{1/2}$) | **1.0 to 1.4 hours** | ~10 hours | 2 to 5 hours | ~9 hours |
| Primary route of excretion | **Bile** | Bile/Kidney | Kidney | Kidney |

# Choose PRANDIN instead of a sulfonylurea

## Low risk of hyperinsulinemia with physiological insulin release

- Insulin levels return toward baseline between meals and during the night

**PRANDIN 24-hour insulin response with 2 meals[5]**




## The PRANDIN advantage

- Mealtime dosing meets rise in postprandial glucose
- Rapid glucose-lowering effect
- Short duration of action
- Low risk of severe hypoglycemia*
- May be used in patients with renal impairment†

* In 1-year, controlled trials comparing PRANDIN (n=1228) with sulfonylureas (n=498) for efficacy and safety, none of the PRANDIN-treated patients with symptomatic hypoglycemia developed coma or required hospitalization. Hypoglycemia was reported in 16% of PRANDIN-treated patients and 20% of patients treated with sulfonylureas (glyburide and glipizide).

† No initial dose adjustment required; subsequent dosing increases should be made carefully.

**References: 1.** Package insert for PRANDIN® (repaglinide) TABLETS, Novo Nordisk Pharmaceuticals, Inc. **2.** Package insert for DiaBeta® (glyburide), Hoechst Marion Roussel; and Glynase® (glyburide), Pharmacia & Upjohn. **3.** Package insert for Glucotrol XL® (glipizide), Pfizer Inc. **4.** Package insert for Amaryl® (glimepiride), Hoechst Marion Roussel. **5.** Data on file. Novo Nordisk Pharmaceuticals, Inc.