

# CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

**APPLICATION NUMBER:**

**11-641/ S-058**

**Trade Name:** Diabinese 100 mg and 250 mg tablets

**Generic Name:** Chlorpropamide

**Sponsor:** Pfizer, Inc.

**Approval Date:** May 16, 2002

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**11-641/s058**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**11-641 / S-058**

**APPROVAL LETTER**



Food and Drug Administration  
Rockville MD 20857

NDA 11-641/S-058

NDA 11-641/S-060

Pfizer Inc.

Attention: Michelle Campbell, R.Ph.  
Director, Worldwide Regulatory Strategy  
235 E. 42nd Street 150/7/12  
New York, NY 10017

Dear Ms. Campbell:

Please refer to your supplemental new drug applications submitted August 2, 1999 (S-058), and May 23, 2001 (S-060), received August 3, 1999, and May 24, 2001, respectively, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diabinese<sup>®</sup> (chlorpropamide) Tablets, USP.

We acknowledge receipt of your submissions dated June 4, 2001 (S-060) and June 19, 2001 (S-058).

Supplement-058 provides for the addition of a **Geriatric Use** subsection to the **PRECAUTIONS** section of the package insert. Supplement-060 provides for revisions to the *Carcinogenesis, Mutagenesis, and Impairment of Fertility* paragraph of the **DRUG INTERACTIONS** section of the package insert.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted April 16, 2002). Accordingly, these supplemental applications are approved effective on the date of this letter.

**Note:** Section 126 of Title F of the 1997 Food and Drug Administration Modernization Act amends section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353(b)(4)) to require, at a minimum, that the label of prescription products contain the symbol "Rx only." According to the FDA guidance entitled, *Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 - Elimination of Certain Labeling Requirements* (Issued 7/1998), the "Rx only" symbol is not required for package insert labeling, if located on the carton/container labeling. However, should a manufacturer choose to include the symbol, the Agency prefers that the symbol be located in the title section. The "Rx only" symbol for this package insert is located at the end of the HOW SUPPLIED section of the package insert, rather than at the beginning. The "Rx only" symbol should be relocated to the title section of the package insert. This can be implemented at the next printing and the Agency notified in the annual report.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call James Cross, Regulatory Project Manager, at 301-827-6381.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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David Orloff

5/16/02 04:07:04 PM

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**NDA 11-641 / S-058**

**APPROVABLE LETTER(S)**

Food and Drug  
Administration  
Rockville MD 20857

NDA 11-641/S-058

Pfizer Pharmaceuticals  
Attention: Craig Audet  
Director/Team Leader  
235 East 42nd Street  
New York, NY 10017-5755

Dear Mr. Audet:

Please refer to your supplemental new drug application dated August 2, 1999, received August 3, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diabense (chlorpropamide) Tablets, 100 mg and 250 mg.

This supplement proposes changes to add a **Geriatric Use** subsection to the **PRECAUTIONS** section of the package insert.

We have completed the review of this application, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit labeling revised to include the following:

The safety and effectiveness of Diabense in patients aged 65 and over has not been properly evaluated in clinical studies. Adverse event reporting suggests that elderly patients may be more prone to developing hypoglycemia and/or hyponatremia when using Diabense. Although the underlying mechanisms are unknown, abnormal renal function, drug interaction, and poor nutrition appear to contribute to these events.

Also, you should revise the following statement, "**CAUTION:** Federal law prohibits dispensing without prescription." to read, "Rx only."

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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David Orloff  
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**CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER***

**NDA 11-641/s058**

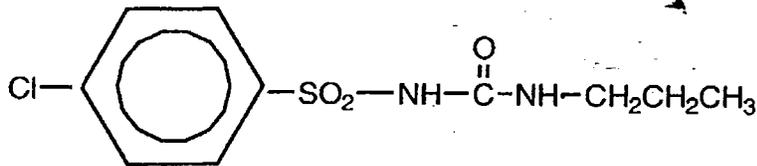
**APPROVED LABELING**

69-2141-00-5

**DIABINESE<sup>®</sup>**  
**(chlorpropamide)**  
**TABLETS, USP**  
**For Oral Use**

**DESCRIPTION**

DIABINESE<sup>®</sup> (chlorpropamide), is an oral blood-glucose-lowering drug of the sulfonylurea class. Chlorpropamide is 1-[(p-Chlorophenyl)sulfonyl]-3-propylurea,  $C_{10}H_{13}ClN_2O_3S$ , and has the structural formula:



Chlorpropamide is a white crystalline powder, that has a slight odor. It is practically insoluble in water at pH 7.3 (solubility at pH 6 is 2.2 mg/ml). It is soluble in alcohol and moderately soluble in chloroform. The molecular weight of chlorpropamide is 276.74. DIABINESE is available as 100 mg and 250 mg tablets.

Inert ingredients are: alginic acid; Blue 1 Lake; hydroxypropyl cellulose; magnesium stearate; precipitated calcium carbonate; sodium lauryl sulfate; starch.

**CLINICAL PHARMACOLOGY**

DIABINESE appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which DIABINESE lowers blood glucose during long-term administration has not been clearly established. Extra-pancreatic effects may play a part in the mechanism of action of oral sulfonylurea hypoglycemic drugs. While chlorpropamide is a sulfonamide derivative, it is devoid of antibacterial activity.

DIABINESE may also prove effective in controlling certain patients who have experienced primary or secondary failure to other sulfonylurea agents.

A method developed which permits easy measurement of the drug in blood is available on request.

Chlorpropamide does not interfere with the usual tests to detect albumin in the urine.

DIABINESE is absorbed rapidly from the gastrointestinal tract. Within one hour after a single oral dose, it is readily detectable in the blood, and the level reaches a maximum within two to four hours. It undergoes metabolism in humans and it is excreted in the urine as unchanged drug and as hydroxylated or hydrolyzed metabolites. The biological half-life of chlorpropamide averages about 36 hours. Within 96 hours, 80-90% of a single oral dose is excreted in the urine. However, long-term administration of therapeutic doses does not result in undue accumulation in the blood, since absorption and excretion rates become stabilized in about 5 to 7 days after the initiation of therapy.

DIABINESE exerts a hypoglycemic effect in healthy subjects within one hour, becoming maximal at 3 to 6 hours and persisting for at least 24 hours. The potency of chlorpropamide is approximately six times that of tolbutamide. Some experimental results suggest that its increased duration of action may be the result of slower excretion and absence of significant deactivation.

#### INDICATIONS AND USAGE

DIABINESE is indicated as an adjunct to diet to lower the blood glucose in patients with type 2 diabetes whose hyperglycemia cannot be controlled by diet alone.

In initiating treatment for non-insulin-dependent diabetes, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered. Use of DIABINESE must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone may be transient, thus requiring only short-term administration of DIABINESE.

During maintenance programs, DIABINESE should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations.

In considering the use of DIABINESE in asymptomatic patients, it should be recognized that controlling the blood glucose in non-insulin-dependent diabetes, has not been definitely

established to be effective in preventing the long-term cardiovascular or neural complications of diabetes.

### CONTRAINDICATIONS

DIABINESE is contraindicated in patients with:

1. Known hypersensitivity to any component of this medicine.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
3. Type 1 diabetes.

### WARNINGS

#### SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

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 (*Diabetes*, 19 [supp. 2]:747-830, 1970).

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 2½ 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 over-all 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 DIABINESE 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.

## PRECAUTIONS

### General

*Hypoglycemia:* All sulfonylurea drugs including chlorpropamide are capable of producing severe hypoglycemia, which may result in coma, and may require hospitalization. Patients experiencing hypoglycemia should be managed with appropriate glucose therapy and be monitored for a minimum of 24 to 48 hours (see Overdosage section). Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Regular, timely carbohydrate intake is important to avoid hypoglycemic events occurring when a meal is delayed or insufficient food is eaten or carbohydrate intake is unbalanced. Renal or hepatic insufficiency may affect the disposition of DIABINESE and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Because of the long half-life of chlorpropamide, patients who become hypoglycemic during therapy require careful supervision of the dose and frequent feedings for at least 3 to 5 days. Hospitalization and intravenous glucose may be necessary.

*Loss of control of blood glucose:* When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue DIABINESE and administer insulin.

The effectiveness of any oral hypoglycemic drug, including DIABINESE, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

### Geriatric Use

The safety and effectiveness of DIABINESE in patients aged 65 and over has not been properly evaluated in clinical studies. Adverse event reporting suggests that elderly patients may be more prone to developing hypoglycemia and/or hyponatremia when using DIABINESE. Although the underlying mechanisms are unknown, abnormal renal function, drug interaction and poor nutrition appear to contribute to these events.

## INFORMATION FOR PATIENTS

Patients should be informed of the potential risks and advantages of DIABINESE and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Patients should be instructed to contact their physician promptly if they experience symptoms of hypoglycemia or other adverse reactions.

### **LABORATORY TESTS**

Blood glucose should be monitored periodically. Measurement of glycosylated hemoglobin should be performed and goals assessed by the current standard of care.

### **DRUG INTERACTIONS**

#### **The following products can lead to hypoglycemia:**

The hypoglycemic action of sulfonylurea may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving DIABINESE, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving DIABINESE, the patient should be observed closely for loss of control.

*Miconazole:* A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with intravenous, topical, or vaginal preparations of miconazole is not known.

*Alcohol:* In some patients, a disulfiram-like reaction may be produced by the ingestion of alcohol. Moderate to large amounts of alcohol may increase the risk of hypoglycemia (ref.1), (ref. 2).

#### **The following products can lead to hyperglycemia:**

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.

When such drugs are administered to a patient receiving DIABINESE, the patient should be closely observed for loss of control. When such drugs are withdrawn from a patient receiving DIABINESE, the patient should be observed closely for hypoglycemia.

Since animal studies suggest that the action of barbiturates may be prolonged by therapy with chlorpropamide, barbiturates should be employed with caution.

*Carcinogenesis, Mutagenesis, Impairment of Fertility:* Studies with DIABINESE have not been conducted to evaluate carcinogenic or mutagenic potential.

Rats treated with continuous DIABINESE therapy for 6 to 12 months showed varying degrees of suppression of spermatogenesis at a dose level of 250 mg/kg (five times the human dose based on body surface area). The extent of suppression seemed to follow that of growth retardation associated with chronic administration of high-dose DIABINESE in rats. The human dose of chlorpropamide is 500 mg/day (300 mg/M<sup>2</sup>). Six- and 12-month toxicity work in the dog and rat, respectively, indicates the 150 mg/kg is well tolerated. Therefore, the safety margins based upon body surface area comparisons are three times human exposure in the rat and 10 times human exposure in the dog.

### **Pregnancy**

#### *Teratogenic Effects:*

Pregnancy Category C. Animal reproductive studies have not been conducted with DIABINESE. It is also not known whether DIABINESE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. DIABINESE should be given to a pregnant woman only if the potential benefits justify the potential risk to the patient and fetus.

Because data suggest that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

#### *Nonteratogenic Effects:*

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. If DIABINESE is used during pregnancy, it should be discontinued at least one month before the expected delivery date and other therapies instituted to maintain blood glucose levels as close to normal as possible.

*Nursing Mothers:* An analysis of a composite of two samples of human breast milk, each taken five hours after ingestion of 500 mg of chlorpropamide by a patient, revealed a concentration of 5 mcg/ml. For reference, the normal peak blood level of chlorpropamide after a single 250 mg dose is 30 mcg/ml. Therefore, it is not recommended that a woman breast feed while taking this medication.

*Use in Children:* Safety and effectiveness in children have not been established.

*Ability to Drive and Use Machines:* The effect of DIABINESE on the ability to drive or operate machinery has not been studied. However, there is no evidence to suggest that DIABINESE may

affect these abilities. Patients should be aware of the symptoms of hypoglycemia and take caution while driving and operating machinery.

## ADVERSE REACTIONS

*Body as a Whole:* Disulfiram-like reactions have rarely been reported with DIABENESE (see DRUG INTERACTIONS).

*Central and Peripheral Nervous System:* Dizziness (ref. 3) and headache (ref. 4).

*Hypoglycemia:* See PRECAUTIONS and OVERDOSAGE sections.

*Gastrointestinal:* Gastrointestinal disturbances are the most common reactions; nausea has been reported in less than 5% of patients, and diarrhea, vomiting, anorexia, and hunger in less than 2%. Other gastrointestinal disturbances have occurred in less than 1% of patients including proctocolitis. They tend to be dose-related and may disappear when dosage is reduced.

*Liver/Biliary:* Cholestatic jaundice may occur rarely; DIABENESE should be discontinued if this occurs. Hepatic porphyria and disulfiram-like reactions have been reported with DIABENESE.

*Skin/Appendages:* Pruritus has been reported in less than 3% of patients. Other allergic skin reactions, e.g., urticaria and maculopapular eruptions have been reported in approximately 1% or less of patients. These may be transient and may disappear despite continued use of DIABENESE; if skin reactions persist the drug should be discontinued.

As with other sulfonylureas, porphyria cutanea tarda and photosensitivity reactions have been reported.

Skin eruptions rarely progressing to erythema multiforme and exfoliative dermatitis have also been reported.

*Hematologic Reactions:* Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, pancytopenia, and eosinophilia have been reported with sulfonylureas.

*Metabolic/Nutritional Reactions:* Hypoglycemia (see PRECAUTIONS and OVERDOSAGE sections). Hepatic porphyria and disulfiram-like reactions have been reported with DIABENESE. See DRUG INTERACTIONS section.

*Endocrine Reactions:* On rare occasions, chlorpropamide has caused a reaction identical to the syndrome of inappropriate antidiuretic hormone (ADH) secretion. The features of this syndrome result from excessive water retention and include hyponatremia, low serum osmolality, and high urine osmolality. This reaction has also been reported for other sulfonylureas.

## OVERDOSAGE

Overdosage of sulfonylureas including DIABINESE can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours since hypoglycemia may recur after apparent clinical recovery.

## DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of type 2 diabetes with DIABINESE or any other hypoglycemic agent. The patient's blood glucose must be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of an adequate blood glucose lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels may also be of value in monitoring the patient's response to therapy.

Short-term administration of DIABINESE may be sufficient during periods of transient loss of control in patients usually controlled well on diet.

The total daily dosage is generally taken at a single time each morning with breakfast. Occasionally cases of gastrointestinal intolerance may be relieved by dividing the daily dosage. **A LOADING OR PRIMING DOSE IS NOT NECESSARY AND SHOULD NOT BE USED.**

**Initial Therapy:** 1. The mild to moderately severe, middle-aged, stable type 2 diabetes patient should be started on 250 mg daily. In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions (see PRECAUTIONS section). Older patients should be started on smaller amounts of DIABINESE, in the range of 100 to 125 mg daily.

2. No transition period is necessary when transferring patients from other oral hypoglycemic agents to DIABINESE. The other agent may be discontinued abruptly and chlorpropamide started at once. In prescribing chlorpropamide, due consideration must be given to its greater potency.

Many mild to moderately severe, middle-aged, stable type 2 diabetes patients receiving insulin can be placed directly on the oral drug and their insulin abruptly discontinued. For patients requiring more than 40 units of insulin daily, therapy with DIABINESE may be initiated with a

50 per cent reduction in insulin for the first few days, with subsequent further reductions dependent upon the response.

During the initial period of therapy with chlorpropamide, hypoglycemic reactions may occasionally occur, particularly during the transition from insulin to the oral drug. Hypoglycemia within 24 hours after withdrawal of the intermediate or long-acting types of insulin will usually prove to be the result of insulin carry-over and not primarily due to the effect of chlorpropamide.

During the insulin withdrawal period, the patient should self-monitor glucose levels at least three times daily. If they are abnormal, the physician should be notified immediately. In some cases, it may be advisable to consider hospitalization during the transition period.

Five to seven days after the initial therapy, the blood level of chlorpropamide reaches a plateau. Dosage may subsequently be adjusted upward or downward by increments of not more than 50 to 125 mg at intervals of three to five days to obtain optimal control. More frequent adjustments are usually undesirable.

**Maintenance Therapy:** Most moderately severe, middle-aged, stable type 2 diabetes patients are controlled by approximately 250 mg daily. Many investigators have found that some milder diabetics do well on daily doses of 100 mg or less. Many of the more severe diabetics may require 500 mg daily for adequate control. PATIENTS WHO DO NOT RESPOND COMPLETELY TO 500 MG DAILY WILL USUALLY NOT RESPOND TO HIGHER DOSES. MAINTENANCE DOSES ABOVE 750 mg DAILY SHOULD BE AVOIDED.

#### HOW SUPPLIED

Strength	Tablet Description	Tablet Code	NDC	Package Size
DIABINESE® (chlorpropamide) 100 mg	Blue, D-shaped, scored	393	0069-3930-66	100's
DIABINESE® (chlorpropamide) 250 mg	Blue, D-shaped, scored	394	0069-3940-66 0069-3940-82	100's 1000's

RECOMMENDED STORAGE: Store below 86°F (30°C).

#### REFERENCES

1. USP: Drug Information for the Health Care Professional (21<sup>st</sup> Edition) 2001, pg 308.
2. Hansten PD and Horm JR. Drug Interactions Analysis and Management 2000 pg. 308.
3. Worldwide Labeling Safety Report: Dizziness and Chlorpropamide (22Mar2002).
4. Worldwide Labeling Safety Report: Headache and Chlorpropamide (22Mar2002).

**Rx only**

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**Pfizer Labs**

Division of Pfizer Inc, NY, NY 10017

69-2141-00-5

Revised August 2002

**CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***  
**NDA 11-641 / S-058**

**MEDICAL REVIEW(S)**

NDA: #11641 Supplement: SLR-058  
Drug Name: Trade: Diabinese Generic: Chlorpropamide  
Sponsor: Pfizer  
Drug Classification: Anti-diabetic  
Review: #1 Submission: Paper: 8/2/99 Electronic: None  
Indication: Geriatric Labeling

#### Introduction

Diabinese is an insulin secretagogue of the sulfonylurea variety. The drug is ionically bound to albumin, unlike the second generation of sulfonylures. The drug is rapidly absorbed, and peak values are observed between 1 and 4 hours post dosing. The biological half-life is approximately 36 hours. Most of the drug is excreted in the urine within 96 hours. Drug excretion occurs as unchanged drug or hydroxylated or hydrolyzed metabolites in the urine. Some of the metabolites are thought to be active. Undue accumulation does not occur in normal volunteers because absorption and excretion equilibrate at 5—7 days.

The efficacy for lowering glucose is thought to be greater for chlorpropamide than that of other first generation agents: >tolinazimide >tolbutamide >acetohexamide, but is thought to be similar to that of the second generation agent, glyburide. Glycemic control was enhanced by the long half-life which permitted once daily dosing, but the long half-life was sufficiently long that some patients developed prolonged hypoglycemia. This was particularly problematic in infirm or hospitalized patients in whom oral or parenteral intake was less than usual. Deaths secondary to this mechanism were reported. Other notable drug complications were cholestasis and inappropriate anti-diuretic hormone (ADH) release and a disulfiram-like reaction. SIADH may be related to renal sensitivity. With the advent of second generation sulfonylureas, with comparable potency and extended, but not prolonged, half-lives, the use of chlorpropamide has declined.

#### Pharmaceutical Sponsor Objective

The sponsor has proposed meeting their regulatory obligations for geriatric labeling with the following label:



#### Data Base

The sponsor provided information derived from spontaneous adverse event reports and a partial literature review.

a--The adverse event data included 654 events divided among patients >65 years of age (n=150 persons; 232 events), >12 and <65 years of age (n=173 persons; 284 events), and those without a designated age in the report (n=83 persons; 138 events). The relative

distribution of the adverse events was similar for all three groups. No demographic data on drug use were presented.

b—The literature review is summarized below:

i--Sartor et al. published single dose (250 mg) pharmacokinetic (PK) data from 9 young, male volunteers (23—38 years) and 8 male and female volunteers (74—75 years). They reported no differences in drug levels for 48 hours. No data beyond 48 hours were presented. No multi-day dosing PK assessments were presented.

ii--Davis et al. reported decreased free water clearance in subjects greater than 60 years of age compared to younger subjects if they were using chlorpropamide. These age related differences were not observed with tolazamide. These free water clearance changes are consistent with reports of hyponatremia and may possibly be enhanced with hydrochlorothiazide (HCTZ) and/or ACE inhibitors. The literature is conflicted about the latter. (See references by Chan, Hirokawa, and Kadowaki.)

iii--Sloan et al. reported more hyponatremia in nursing-home patients treated with chlorpropamide than when they were treated with tolazamide.

iv--Kadowaki et al. reported that hyponatremia was more common in patients using chlorpropamide than in patients using tolbutamide or glyburide. The patients who became hypoglycemic were older as a cohort than the normonatremic patients.

v--Seltzer reviewed 1418 cases of drug-related hypoglycemia. Most of the cases were associated with glyburide and chlorpropamide use. Age was reported to be a risk factor. Berger et al. confirmed these data. They identified impaired renal function and possibly drug interactions as risk factors.

vi--Shorr et al. assessed the relative risk of hypoglycemia for various anti-diabetic agents in geriatric Medicaid patients: Chlorpropamide and glyburide were comparable.

Tolazamide and glipizide had comparable levels of hypoglycemia that were less than those of glyuride and chlorpropamide, but more than that of tolbutamide. (N.B. This study was funded in part by the FDA: #FD-U-000073.) In another publication, these same authors identified risk factors for hypoglycemia: recent hospital discharge, being Afro-American, use of five or more medications, and advanced age within the Medicare cohort. (The group did not compare patients less than 65 years with those 65 or older.)

vii--Several authors (Stepka et al., Schen and Benaroya) suggested that hypoglycemia in the elderly may be complicated by cardiovascular events.

viii--Dr. Ann Peters and the reknowned diabetologist, Dr. Mayer Davidson, reviewed sulfonylurea anti-diabetic agents. They concluded that chlorpropamide was the most dangerous of the agents available in 1990 and recommended against its use in the elderly. Dr. John Gerich presented concordant data.

c--No new data on drug interactions were presented. The label indicates that miconazoles, NSAIDs, salicylates, sulfonamides, chloramphenicol, probenacid, coumarins, MAOIs, beta-blockers, and protein bound drugs may potentiate hypoglycemia. No data were presented on whether this interaction is related to metabolism by the cytochrome P450 system.

Conclusions

The limited data suggest that chlorpropamide is more problematic for older patients—especially the very old. Hyponatremia and hypoglycemia appear to be the most significant problems. Furthermore, the sequelae of these adverse events may be more devastating in the geriatric population. Alterations in renal function secondary to age, diabetes, and the duration of diabetes may contribute to hyponatremia and hypoglycemia. The relationship of renal function to drug-related hyponatremia is somewhat more established than the relationship of renal function to drug-related hypoglycemia, but would benefit from further assessment. The pharmacokinetic study that was presented does not permit us to comment on whether there are age-related differences in drug levels beyond 48 hours or the appearance and disappearance of active metabolites. Nor do the data permit us to comment on age related differences in drug and metabolite levels after multiple doses. Perhaps most importantly, the study does not permit us to comment on chlorpropamide metabolism with concomitant drug use, and it is well known that many older patients are on multiple drugs.

Therefore, the label as delineated by the sponsor is not acceptable. The sponsor should have the option of doing additional studies:

- a--Drug interaction studies
  - b--Multiple-dose PK studies in young, old, and very old patients
  - c--Clinical comparison of hypoglycemia and hyponatremia in young and old patients.
- This study could be done using the Tennessee Medicaid data base used by Shorr et al. or a comparable Medicare data base. The control, or younger patients, could be obtained by using state medical assistance data bases. The data bases are not entirely comparable, but these limitations may be acceptable.

In lieu of these extra studies, the sponsor could accept the following label:



Regulatory Conclusions:

The proposed label is not approvable without substantiating studies.

Elizabeth Koller, M.D. 2/15/01

Enclosures

*Geriatric Pharmaceutical Care Guidelines 1997/98 edition.* Clinical Evaluations: Philadelphia College of Pharmacy and Sciences. The OmniCare Formulary.

## References

- 1--Berger W, Caduff F, Pasquel M, Rump A. *The relatively frequent incidence of severe sulfonylurea-induced hypoglycemia in the last 25 years in Switzerland: results of 2 surveys in Switzerland in 1969 and 1984.* Schweiz Med Wochenschr 1986;116:145-51.
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- 3--Davis FB, Van Sin A, Davis PJ, Edwards L. *Urinary diluting capacity in elderly diabetic subjects.* Experimental Gerontology 1986;21:407-412.
- 4--Gerich JE. *Oral hypoglycemic agents.* N Engl J Med 1989;321:1231-1245.
- 5--Hirokawa CA, Gray DR. *Chlorpropamide-induced hyponatremia in the veteran population.* Ann Pharmacother 1992;26:1243-1244.
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- 7--Peters AL, Davidson MB. *Use of sulfonylurea agents in older diabetic patients.* Clin Geriatr Med 1990;6:903-921.
- 8--Sartor G, Melander A, Schersten B, Wahlin-Boll E. *Influence of food and age on the single-dose pharmacokinetics and effects of tolbutamide and chlorpropamide.* Eur J Clin Pharmacol 1980;17:285-293.
- 9--Schen RJ, Benaroya Y. *Hypoglycemic coma due to chlorpropamide: observations on 22 patients.* Age and Ageing 1976;5:31-36.
- 10--Seltzer HS. *Drug-induced hypoglycemia; a review of 1418 cases.* Endocrinol Metab Clin North Am 1989;18:163-183.
- 11--Shorr RI, Ray WA, Daugherty JR, Griffin MR. *Individual sulfonylureas and serious hypoglycemia in older people.* J Am Geriatr Soc 1996;44:751-755.
- 12--Shorr RI, Ray WA, Daugherty JR, Griffin MR. *Incidence and risk factors for serious hypoglycemia in older patients using insulin or hypoglycemia.* Arch Intern Med 1997;157:1681-1686.
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- 14--Sloan RW, Kreider RM, Luderer JR. *The effect of chlorpropamide hyponatremia on mental status in a nursing home population.* J Fam Pract 1983;16:937-942.
- 15--Stepka M, Rogala H, Czysyk A. *Hypoglycemia: a major problem in the management of diabetes in the elderly.* Aging Clin Exp Res 1993;5:117-121.

APPEARS THIS WAY  
ON ORIGINAL

/s/

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Elizabeth Koller  
2/27/01 02:32:41 PM  
MEDICAL OFFICER

Saul Malozowski  
2/27/01 05:53:54 PM  
MEDICAL OFFICER

NDA: #11641 Supplement: SLR-058

Drug Name: Trade: Diabinese Generic: Chlorpropamide

Sponsor: Pfizer

Drug Classification: Anti-diabetic

Review: #1 Submission: Paper: 8/2/99 Electronic: None

Indication: Geriatric Labeling

Alternative label wording proposed by Saul Malozowski, M.D., Ph.D.:

*The safety and effectiveness of Diabinese in patients aged 65 and over has not been properly evaluated in clinical studies. Adverse event reporting suggests that elderly patients may be more prone to developing hypoglycemia and/or hyponatremia when using Diabinese. Although the underlying mechanisms are unknown, abnormal renal function, drug interaction, and poor nutrition appear to contribute to these events.*

Elizabeth Koller, M.D. 2/27/01

**APPEARS THIS WAY  
ON ORIGINAL**

/s/

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Elizabeth Koller  
2/27/01 02:36:02 PM  
MEDICAL OFFICER

Saul Malozowski  
2/27/01 05:54:49 PM  
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**11-641/ S-058**

**ADMINISTRATIVE DOCUMENTS**  
**AND**  
**CORRESPONDENCE**

Division of Metabolic and Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

Application Number: 11-641/S-058

Name of Drug: Diabinese® (chlorpropamide) Tablets, USP 100 mg and 250 mg.

Sponsor: Pfizer/Warner-Lambert

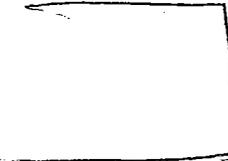
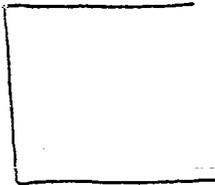
Material Reviewed: DRAFT package insert. This was compared to currently approved labeling (SLR-055) for chlorpropamide submitted on February 17, 1987, and approved on May 12, 1987.

Submission Date: August 2, 1999

Receipt Date: August 3, 1999.

PM review date: May 16, 2001

**Background and Summary Description:** Diabinese Tablets, approved 10/28/58, is currently approved for use as an adjunct to diet in non-insulin dependent (Type 2) diabetes whose hyperglycemia cannot be controlled by diet alone. Supplement 058 proposes an addition to the package insert to add a **Geriatric Use** subsection under the **PRECAUTIONS** section. The company proposes the following language:



**Review:**

The submitted draft labeling was compared to the currently approved labeling (S-055), Identifier 69-2141-37-9, revised June 1986, approved February 17, 1987. The draft submission, is identical to the approved labeling except for the following sections:

1. **DESCRIPTION** section: A paragraph that lists the inert ingredients was added. It reads, "Inert ingredients are: alginic acid; Blue 1 Lake; hydroxypropyl cellulose; magnesium stearate; precipitated calcium carbonate; sodium lauryl sulfate; starch."
2. **HOW SUPPLIED** section: For both the 100 mg and 250 mg tablets, there are 2 different NDC numbers listed for each presentation (for example, the 100 count bottle of the 100 mg tablets). These NDC numbers differ only in the first four digits ("0069" and "0663"). Only those NDC numbers beginning with "0663" appear in the currently approved labeling. NDC numbers with the digits "0069" as the first 4 digits, indicate that the tablets were manufactured   
 In a conversation with Mr. Craig Audet (4/17/01),

**NDC Search Results on 00069**

**Firm Name:** PFIZER LABORATORIES DIV PFIZER INC  
**Address Header:** ATTN MARIANNE KOPELMAN 150 3 46  
**Street:** 235 EAST 42ND ST  
**PO Box:**  
**Foreign Address:**  
**City, State Zip** NEW YORK, NY 10017  
**Country Name** UNITED STATES

[Return to National Drug Code Directory Home Page](#)

he stated that Pfizer is c

According to the February 27, 2001 medical review, the **Geriatric Use** subsection should read as follows:

The safety and effectiveness of Diabinese in patients aged 65 and over has not been properly evaluated in clinical studies. Adverse event reporting suggests that elderly patients may be more prone to developing hypoglycemia and/or hyponatremia when using Diabinese. Although the underlying mechanisms are unknown, abnormal renal function, drug interaction, and poor nutrition appear to contribute to these events.

**Conclusion:** An approvable letter should be drafted, pending revision of the **Geriatric Use** subsection as stated above. In addition, the firm should be requested to replace the statement, "**CAUTION:** Federal law prohibits dispensing without prescription," with "Rx only," (In their 4/4/01 annual report, the sponsor notified the Agency of their intent to make this change).

Jena Weber, PM  
DiabineseS58.doc

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this page is the manifestation of the electronic signature.**  
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/s/

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Jena Weber  
6/7/01 11:55:07 AM  
CSO

David Orloff  
6/8/01 12:05:25 PM  
MEDICAL OFFICER

During an April 23, 2002, telephone conversation between myself and Mr. John Kennedy of Pfizer Inc, I cited a conversation held April 17, 2001 between Ms. Jena Weber of the Division and Mr. Craig Audet of Pfizer Inc.:

Mr. Kennedy confirmed that despite the April 17, 2001, conversation, the NDC numbers listed in the **HOW SUPPLIED** section of the final printed labeling submitted April 16, 2002 are the correct NDC numbers:

- NDC 0069-3930-66: 100 mg tablets, 100 count package
- NDC 0069-3940-66: 250 mg tablets, 100 count package
- NDC 0069-3940-82: 250 mg tablets, 1000 count package

[Note: Section 126 of Title I of the 1997 Food and Drug Administration Modernization Act amends section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353(b)(4)) to require, at a minimum, that the label of prescription products contain the symbol "Rx only." According to the FDA guidance entitled, *Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 - Elimination of Certain Labeling Requirements* (Issued 7/1998), the "Rx only" symbol is not required for package insert labeling, if located on the carton/container labeling. However, should a manufacturer choose to include the symbol, the Agency prefers that the symbol be located in the title section. The "Rx only" symbol for this package insert is located at the end of the HOW SUPPLIED section of the package insert, rather than at the beginning.]

#### Conclusions

Supplements-058 and -060 should be approved on the final printed labeling submitted April 16, 2002. The firm should be informed that the "Rx only" symbol should be relocated to the title section of the package insert. This can be implemented at the next printing and the Agency notified in the annual report.

**APPEARS THIS WAY  
ON ORIGINAL**

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/s/

James Cross  
4/26/02 05:00:51 PM.  
CSO

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**11-641/ S-060**

***Trade Name:*** Diabinese 100 mg and 250 mg tablets

***Generic Name:*** Chlorpropamide

***Sponsor:*** Pfizer, Inc.

***Approval Date:*** May 5, 2002

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**11-641/s060**

## CONTENTS

### Reviews / Information Included in this NDA Review.

<b>Approval Letter</b>	<b>X</b>
<b>Approvable Letter</b>	<b>X</b>
<b>Final Printed Labeling</b>	<b>X</b>
<b>Medical Review(s)</b>	
<b>Chemistry Review(s)</b>	
<b>EA/FONSI</b>	
<b>Pharmacology Review(s)</b>	
<b>Statistical Review(s)</b>	
<b>Microbiology Review(s)</b>	
<b>Clinical Pharmacology/ Biopharmaceutics Review(s)</b>	<b>X</b>
<b>Administrative and Correspondence Document(s)</b>	<b>X</b>

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**11-641 / S-060**

**APPROVAL LETTER**



Food and Drug Administration  
Rockville MD 20857

NDA 11-641/S-058  
NDA 11-641/S-060

Pfizer Inc.  
Attention: Michelle Campbell, R.Ph.  
Director, Worldwide Regulatory Strategy  
235 E. 42nd Street 150/7/12  
New York, NY 10017

Dear Ms. Campbell:

Please refer to your supplemental new drug applications submitted August 2, 1999 (S-058), and May 23, 2001 (S-060), received August 3, 1999, and May 24, 2001, respectively, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diabinese® (chlorpropamide) Tablets, USP.

We acknowledge receipt of your submissions dated June 4, 2001 (S-060) and June 19, 2001 (S-058).

Supplement-058 provides for the addition of a **Geriatric Use** subsection to the **PRECAUTIONS** section of the package insert. Supplement-060 provides for revisions to the *Carcinogenesis, Mutagenesis, and Impairment of Fertility* paragraph of the **DRUG INTERACTIONS** section of the package insert.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted April 16, 2002). Accordingly, these supplemental applications are approved effective on the date of this letter.

**Note:** Section 126 of Title I of the 1997 Food and Drug Administration Modernization Act amends section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353(b)(4)) to require, at a minimum, that the label of prescription products contain the symbol "Rx only." According to the FDA guidance entitled, *Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 - Elimination of Certain Labeling Requirements* (Issued 7/1998), the "Rx only" symbol is not required for package insert labeling, if located on the carton/container labeling. However, should a manufacturer choose to include the symbol, the Agency prefers that the symbol be located in the title section. The "Rx only" symbol for this package insert is located at the end of the HOW SUPPLIED section of the package insert, rather than at the beginning. The "Rx only" symbol should be relocated to the title section of the package insert. This can be implemented at the next printing and the Agency notified in the annual report.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call James Cross, Regulatory Project Manager, at 301-827-6381.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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David Orloff  
5/16/02 04:07:04 PM

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*APPLICATION NUMBER:*  
**NDA 11-641 / S-060**

**APPROVABLE LETTER(S)**



Food and Drug Administration  
Rockville MD 20857

NDA 11-641/S-060

Pfizer Inc.  
Attention: Michelle G. Campbell, R.Ph.  
Director, Worldwide Regulatory Strategy  
235 E. 42nd Street 150/7/12  
New York, NY 10017

Dear Ms. Campbell:

We acknowledge receipt of your supplemental new drug application dated May 23, 2001, received May 24, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diabinese (chlorpropamide) Tablets.

We also refer to your amendment dated June 4, 2001, submitted in response to our request for additional information on the source of the calculation for the exposure multiple in the animal toxicity data.

This supplemental application, submitted under 21CFR 314.70(c) as a "Changes Being Effected" proposes the following revisions to the "Carcinogenesis, Mutagenesis, and Impairment of Fertility" subsection of the "Drug Interactions" section of the label:

1. Delete information from dog toxicity studies and replace with the following: "Studies with Diabinese have not been performed to evaluate carcinogenic or mutagenic potential."
2. Increase the upper dosing levels at which the suppression of spermatogenesis has been observed in rats.
3. Add information on the safety factor of Diabinese based on exposure in rat and dog versus human.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) revised as follows:

*Carcinogenesis, Mutagenesis, Impairment of Fertility:*

Studies with Diabinese have not been conducted to evaluate carcinogenic or mutagenic potential. Rats treated with continuous Diabinese therapy for 6 to 12 months showed varying degrees of suppression of spermatogenesis at a dose level of 250 mg/kg (5 times human dose based on body surface area). The extent of suppression seemed to follow that of growth retardation associated with chronic administration of high-dose Diabinese in rats. The human dose of

chloropropamide is 500 mg/day (300 mg/M<sup>2</sup>). Six and twelve month toxicity studies in the dog and rat, respectively, indicate 150 mg/kg is well tolerated. Therefore, the safety margins based upon body surface area comparisons are 3 times human exposure in the rat and 10 times human exposure in the dog.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, call James T. Cross, Regulatory Project Manager, at 301-480-8174.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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David Orloff  
6/29/01 10:42:06 AM

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**NDA 11-641/s060**

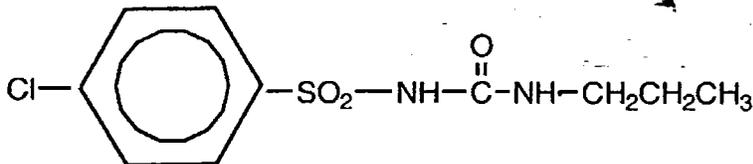
**APPROVED LABELING**

69-2141-00-5

**DIABINESE<sup>®</sup>**  
**(chlorpropamide)**  
**TABLETS, USP**  
**For Oral Use**

**DESCRIPTION**

DIABINESE<sup>®</sup> (chlorpropamide), is an oral blood-glucose-lowering drug of the sulfonylurea class. Chlorpropamide is 1-[(p-Chlorophenyl)sulfonyl]-3-propylurea, C<sub>10</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>3</sub>S, and has the structural formula:



Chlorpropamide is a white crystalline powder, that has a slight odor. It is practically insoluble in water at pH 7.3 (solubility at pH 6 is 2.2 mg/ml). It is soluble in alcohol and moderately soluble in chloroform. The molecular weight of chlorpropamide is 276.74. DIABINESE is available as 100 mg and 250 mg tablets.

Inert ingredients are: alginic acid; Blue 1 Lake; hydroxypropyl cellulose; magnesium stearate; precipitated calcium carbonate; sodium lauryl sulfate; starch.

**CLINICAL PHARMACOLOGY**

DIABINESE appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which DIABINESE lowers blood glucose during long-term administration has not been clearly established. Extra-pancreatic effects may play a part in the mechanism of action of oral sulfonylurea hypoglycemic drugs. While chlorpropamide is a sulfonamide derivative, it is devoid of antibacterial activity.

DIABINESE may also prove effective in controlling certain patients who have experienced primary or secondary failure to other sulfonylurea agents.

A method developed which permits easy measurement of the drug in blood is available on request.

Chlorpropamide does not interfere with the usual tests to detect albumin in the urine.

DIABINESE is absorbed rapidly from the gastrointestinal tract. Within one hour after a single oral dose, it is readily detectable in the blood, and the level reaches a maximum within two to four hours. It undergoes metabolism in humans and it is excreted in the urine as unchanged drug and as hydroxylated or hydrolyzed metabolites. The biological half-life of chlorpropamide averages about 36 hours. Within 96 hours, 80-90% of a single oral dose is excreted in the urine. However, long-term administration of therapeutic doses does not result in undue accumulation in the blood, since absorption and excretion rates become stabilized in about 5 to 7 days after the initiation of therapy.

DIABINESE exerts a hypoglycemic effect in healthy subjects within one hour, becoming maximal at 3 to 6 hours and persisting for at least 24 hours. The potency of chlorpropamide is approximately six times that of tolbutamide. Some experimental results suggest that its increased duration of action may be the result of slower excretion and absence of significant deactivation.

#### INDICATIONS AND USAGE

DIABINESE is indicated as an adjunct to diet to lower the blood glucose in patients with type 2 diabetes whose hyperglycemia cannot be controlled by diet alone.

In initiating treatment for non-insulin-dependent diabetes, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered. Use of DIABINESE must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone may be transient, thus requiring only short-term administration of DIABINESE.

During maintenance programs, DIABINESE should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations.

In considering the use of DIABINESE in asymptomatic patients, it should be recognized that controlling the blood glucose in non-insulin-dependent diabetes, has not been definitely

established to be effective in preventing the long-term cardiovascular or neural complications of diabetes.

### CONTRAINDICATIONS

DIABINESE is contraindicated in patients with:

1. Known hypersensitivity to any component of this medicine.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
3. Type 1 diabetes.

### WARNINGS

#### SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

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 (*Diabetes*, 19 [supp. 2]:747-830, 1970).

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 2½ 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 over-all 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 DIABINESE 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.

## PRECAUTIONS

### General

*Hypoglycemia:* All sulfonylurea drugs including chlorpropamide are capable of producing severe hypoglycemia, which may result in coma, and may require hospitalization. Patients experiencing hypoglycemia should be managed with appropriate glucose therapy and be monitored for a minimum of 24 to 48 hours (see Overdosage section). Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Regular, timely carbohydrate intake is important to avoid hypoglycemic events occurring when a meal is delayed or insufficient food is eaten or carbohydrate intake is unbalanced. Renal or hepatic insufficiency may affect the disposition of DIABINESE and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Because of the long half-life of chlorpropamide, patients who become hypoglycemic during therapy require careful supervision of the dose and frequent feedings for at least 3 to 5 days. Hospitalization and intravenous glucose may be necessary.

*Loss of control of blood glucose:* When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue DIABINESE and administer insulin.

The effectiveness of any oral hypoglycemic drug, including DIABINESE, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

### Geriatric Use

The safety and effectiveness of DIABINESE in patients aged 65 and over has not been properly evaluated in clinical studies. Adverse event reporting suggests that elderly patients may be more prone to developing hypoglycemia and/or hyponatremia when using DIABINESE. Although the underlying mechanisms are unknown, abnormal renal function, drug interaction and poor nutrition appear to contribute to these events.

## INFORMATION FOR PATIENTS

Patients should be informed of the potential risks and advantages of DIABINESE and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Patients should be instructed to contact their physician promptly if they experience symptoms of hypoglycemia or other adverse reactions.

### LABORATORY TESTS

Blood glucose should be monitored periodically. Measurement of glycosylated hemoglobin should be performed and goals assessed by the current standard of care.

### DRUG INTERACTIONS

#### **The following products can lead to hypoglycemia:**

The hypoglycemic action of sulfonylurea may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving DIABINESE, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving DIABINESE, the patient should be observed closely for loss of control.

*Miconazole:* A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with intravenous, topical, or vaginal preparations of miconazole is not known.

*Alcohol:* In some patients, a disulfiram-like reaction may be produced by the ingestion of alcohol. Moderate to large amounts of alcohol may increase the risk of hypoglycemia (ref.1), (ref. 2).

#### **The following products can lead to hyperglycemia:**

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.

When such drugs are administered to a patient receiving DIABINESE, the patient should be closely observed for loss of control. When such drugs are withdrawn from a patient receiving DIABINESE, the patient should be observed closely for hypoglycemia.

Since animal studies suggest that the action of barbiturates may be prolonged by therapy with chlorpropamide, barbiturates should be employed with caution.

*Carcinogenesis, Mutagenesis, Impairment of Fertility:* Studies with DIABINESE have not been conducted to evaluate carcinogenic or mutagenic potential.

Rats treated with continuous DIABINESE therapy for 6 to 12 months showed varying degrees of suppression of spermatogenesis at a dose level of 250 mg/kg (five times the human dose based on body surface area). The extent of suppression seemed to follow that of growth retardation associated with chronic administration of high-dose DIABINESE in rats. The human dose of chlorpropamide is 500 mg/day (300 mg/M<sup>2</sup>). Six- and 12-month toxicity work in the dog and rat, respectively, indicates the 150 mg/kg is well tolerated. Therefore, the safety margins based upon body surface area comparisons are three times human exposure in the rat and 10 times human exposure in the dog.

### **Pregnancy**

#### *Teratogenic Effects:*

Pregnancy Category C. Animal reproductive studies have not been conducted with DIABINESE. It is also not known whether DIABINESE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. DIABINESE should be given to a pregnant woman only if the potential benefits justify the potential risk to the patient and fetus.

Because data suggest that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

#### *Nonteratogenic Effects:*

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. If DIABINESE is used during pregnancy, it should be discontinued at least one month before the expected delivery date and other therapies instituted to maintain blood glucose levels as close to normal as possible.

*Nursing Mothers:* An analysis of a composite of two samples of human breast milk, each taken five hours after ingestion of 500 mg of chlorpropamide by a patient, revealed a concentration of 5 mcg/ml. For reference, the normal peak blood level of chlorpropamide after a single 250 mg dose is 30 mcg/ml. Therefore, it is not recommended that a woman breast feed while taking this medication.

*Use in Children:* Safety and effectiveness in children have not been established.

*Ability to Drive and Use Machines:* The effect of DIABINESE on the ability to drive or operate machinery has not been studied. However, there is no evidence to suggest that DIABINESE may

affect these abilities. Patients should be aware of the symptoms of hypoglycemia and take caution while driving and operating machinery.

## ADVERSE REACTIONS

*Body as a Whole:* Disulfiram-like reactions have rarely been reported with DIABENESE (see DRUG INTERACTIONS).

*Central and Peripheral Nervous System:* Dizziness (ref. 3) and headache (ref. 4).

*Hypoglycemia:* See PRECAUTIONS and OVERDOSAGE sections.

*Gastrointestinal:* Gastrointestinal disturbances are the most common reactions; nausea has been reported in less than 5% of patients, and diarrhea, vomiting, anorexia, and hunger in less than 2%. Other gastrointestinal disturbances have occurred in less than 1% of patients including proctocolitis. They tend to be dose-related and may disappear when dosage is reduced.

*Liver/Biliary:* Cholestatic jaundice may occur rarely; DIABENESE should be discontinued if this occurs. Hepatic porphyria and disulfiram-like reactions have been reported with DIABENESE.

*Skin/Appendages:* Pruritus has been reported in less than 3% of patients. Other allergic skin reactions, e.g., urticaria and maculopapular eruptions have been reported in approximately 1% or less of patients. These may be transient and may disappear despite continued use of DIABENESE; if skin reactions persist the drug should be discontinued.

As with other sulfonylureas, porphyria cutanea tarda and photosensitivity reactions have been reported.

Skin eruptions rarely progressing to erythema multiforme and exfoliative dermatitis have also been reported.

*Hematologic Reactions:* Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, pancytopenia, and eosinophilia have been reported with sulfonylureas.

*Metabolic/Nutritional Reactions:* Hypoglycemia (see PRECAUTIONS and OVERDOSAGE sections). Hepatic porphyria and disulfiram-like reactions have been reported with DIABENESE. See DRUG INTERACTIONS section.

*Endocrine Reactions:* On rare occasions, chlorpropamide has caused a reaction identical to the syndrome of inappropriate antidiuretic hormone (ADH) secretion. The features of this syndrome result from excessive water retention and include hyponatremia, low serum osmolality, and high urine osmolality. This reaction has also been reported for other sulfonylureas.

## OVERDOSAGE

Overdosage of sulfonylureas including DIABINESE can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours since hypoglycemia may recur after apparent clinical recovery.

## DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of type 2 diabetes with DIABINESE or any other hypoglycemic agent. The patient's blood glucose must be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of an adequate blood glucose lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels may also be of value in monitoring the patient's response to therapy.

Short-term administration of DIABINESE may be sufficient during periods of transient loss of control in patients usually controlled well on diet.

The total daily dosage is generally taken at a single time each morning with breakfast. Occasionally cases of gastrointestinal intolerance may be relieved by dividing the daily dosage. A **LOADING OR PRIMING DOSE IS NOT NECESSARY AND SHOULD NOT BE USED.**

**Initial Therapy:** 1. The mild to moderately severe, middle-aged, stable type 2 diabetes patient should be started on 250 mg daily. In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions (see PRECAUTIONS section). Older patients should be started on smaller amounts of DIABINESE, in the range of 100 to 125 mg daily.

2. No transition period is necessary when transferring patients from other oral hypoglycemic agents to DIABINESE. The other agent may be discontinued abruptly and chlorpropamide started at once. In prescribing chlorpropamide, due consideration must be given to its greater potency.

Many mild to moderately severe, middle-aged, stable type 2 diabetes patients receiving insulin can be placed directly on the oral drug and their insulin abruptly discontinued. For patients requiring more than 40 units of insulin daily, therapy with DIABINESE may be initiated with a

50 per cent reduction in insulin for the first few days, with subsequent further reductions dependent upon the response.

During the initial period of therapy with chlorpropamide, hypoglycemic reactions may occasionally occur, particularly during the transition from insulin to the oral drug. Hypoglycemia within 24 hours after withdrawal of the intermediate or long-acting types of insulin will usually prove to be the result of insulin carry-over and not primarily due to the effect of chlorpropamide.

During the insulin withdrawal period, the patient should self-monitor glucose levels at least three times daily. If they are abnormal, the physician should be notified immediately. In some cases, it may be advisable to consider hospitalization during the transition period.

Five to seven days after the initial therapy, the blood level of chlorpropamide reaches a plateau. Dosage may subsequently be adjusted upward or downward by increments of not more than 50 to 125 mg at intervals of three to five days to obtain optimal control. More frequent adjustments are usually undesirable.

**Maintenance Therapy:** Most moderately severe, middle-aged, stable type 2 diabetes patients are controlled by approximately 250 mg daily. Many investigators have found that some milder diabetics do well on daily doses of 100 mg or less. Many of the more severe diabetics may require 500 mg daily for adequate control. PATIENTS WHO DO NOT RESPOND COMPLETELY TO 500 MG DAILY WILL USUALLY NOT RESPOND TO HIGHER DOSES. MAINTENANCE DOSES ABOVE 750 mg DAILY SHOULD BE AVOIDED.

#### HOW SUPPLIED

Strength	Tablet Description	Tablet Code	NDC	Package Size
DIABINESE® (chlorpropamide) 100 mg	Blue, D-shaped, scored	393	0069-3930-66	100's
DIABINESE® (chlorpropamide) 250 mg	Blue, D-shaped, scored	394	0069-3940-66 0069-3940-82	100's 1000's

RECOMMENDED STORAGE: Store below 86°F (30°C).

#### REFERENCES

1. USP: Drug Information for the Health Care Professional (21<sup>st</sup> Edition) 2001, pg 308.
2. Hansten PD and Horm JR. Drug Interactions Analysis and Management 2000 pg. 308.
3. Worldwide Labeling Safety Report: Dizziness and Chlorpropamide (22Mar2002).
4. Worldwide Labeling Safety Report: Headache and Chlorpropamide (22Mar2002).

Rx only

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**Pfizer Labs**

Division of Pfizer Inc, NY, NY 10017

69-2141-00-5

Revised August 2002

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**NDA 11-641 / S-060**

**CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS**  
**REVIEW(S)**



Memorandum

Date: June 20, 2001

To: NDA 11-641 File

From: Jeri El-Hage, Ph.D., Pharmacology Supervisor, HFD-510

Subject: Pharmacology Deficiencies for Diabenese revised labelling

Dr. Ronald Steigerwalt, former Pharmacology Team Leader, sent a fax to Pfizer in February, 1999 requesting revisions to the preclinical sections of the label to more accurately represent the preclinical data. (see SLR 060 dated 5-23-01 for copy of fax)

Pfizer has added the requested statement that no mutagenicity or carcinogenicity assessments have been conducted with Diabenese.

CDER has an ongoing initiative to update labels to current standards when labeling supplements are submitted. Exposure comparisons between animal and human doses are no longer expressed on a mg/kg basis. Ideally, safety margins (exposure ratios) are calculated based upon actual plasma drug exposure data (AUC). For products without toxicokinetics data, safety margins are calculated based on mg/kg dose corrected for body surface area ( $\text{mg}/\text{M}^2$ ). This has been demonstrated to provide data that is more comparable to actual exposures because it corrects for differences in metabolic rate, etc.

Converting doses from mg/kg to  $\text{mg}/\text{M}^2$  requires only a simple mathematical calculation. Therefore, Pfizer's contention in the submission of 6/4/01 that the reference data from the NDA was based upon mg/kg and, therefore, this data presentation is more accurate is not acceptable. **Pfizer should be advised that the labeling revision should express safety margins based upon body surface area ( $\text{mg}/\text{M}^2$  NOT  $\text{Kg}/\text{M}^2$  as stated in their 6/4/01 submission).**

I have calculated the safety margins for the data and provided precisely how we would like to see the label revised as follows:

*Carcinogenesis, Mutagenesis, Impairment of Fertility:*

Studies with Diabenese have not been conducted to evaluate carcinogenic or mutagenic potential.

Rats treated with continuous Diabenese therapy for 6 to 12 months showed varying degrees of suppression of spermatogenesis at a dose level of 250 mg/kg (5 times human dose based on body surface area). The extent of suppression seemed to follow that of growth retardation associated with chronic administration of high-dose Diabenese in rats. The human dose of chlorpropamide is 500 mg/day ( $300 \text{ mg}/\text{M}^2$ ). Six and twelve month toxicity studies in the dog and rat, respectively, indicate 150 mg/kg is well tolerated. Therefore, the safety margins based upon body surface area comparisons are 3 times human exposure in the rat and 10 times human exposure in the dog.

**Calculations upon which safety margins are based.**

Human dose =  $500 \text{ mg/day} \div 60 \text{ kg} = 8 \text{ mg/kg} \times 37 = 300 \text{ mg/M}^2$

NOAEL in rat =  $150 \text{ mg/kg} \times 6 = 900 \text{ mg/M}^2$  (3 times human  $\text{mg/M}^2$  dose)

NOAEL in dog =  $150 \text{ mg/kg} \times 20 = 3000 \text{ mg/M}^2$  (10 times human dose)

**Recommendations:**

Pharmacology continues to recommend that the sponsor update the label to express safety margins based on body surface area ( $\text{mg/M}^2$ ).

Pfizer's justifications for maintaining safety margins based on  $\text{mg/kg}$  in the June 4, 2001 submission are not acceptable. It appears that the doses expressed as NOAEL and toxic doses are appropriate.

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/s/

Jeri El Hage  
6/20/01 10:08:56 AM  
PHARMACOLOGIST

**CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***  
**NDA 11-641 / S-060**

**CORRESPONDENCE**

Division of Metabolic and Endocrine Drug Products (HFD-510)

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 11-641/SLR-058,-060

Name of Drug: Diabinese® (chlorpropamide) Tablets, USP  
Sponsor: Pfizer, Inc.

Material Reviewed:

**Draft Package Insert**

S-058  
Submitted: August 2, 1999  
Received: August 3, 1999

S-060  
Submitted: May 23, 2001  
Received: May 24, 2001

**Final Printed Labeling**

S-058 (Identifier 69-2141-00-4, Revised October 2001)  
Submitted: April 16, 2002  
Received: April 17, 2002

S-060 (Identifier 69-2141-00-4, Revised October 2001)  
Submitted: April 16, 2002  
Received: April 17, 2002

Background and Summary

Supplement 058 (S-058) provides for the addition of a **Geriatric Use** subsection to the **PRECAUTIONS** section of the package insert, as required under 21 CFR 201.57(f)(10). This supplement was approvable on June 8, 2001, pending submission of final printed labeling.

Supplement 060 (S-060) provides for revisions to the *Carcinogenesis, Mutagenesis, and Impairment of Fertility* paragraph of the **DRUG INTERACTIONS** section of the package insert. This supplement was approvable on June 29, 2001, pending submission of final printed labeling.

Review

The final printed labeling (package insert) contains all revisions provided for in both supplements, plus all revisions to the draft labeling requested by the Agency in the approvable letter of each supplement.

In addition to the changes provided for in the provisions of these two supplements, the final printed labeling contains a revised HOW SUPPLIED section. The following NDC numbers have been deleted from the final printed labeling:

S-058: NDC 0663-3930-66 100 mg tablets (100 count package).  
NDC 0663-3930-73 100 mg tablets (500 count package).  
NDC 0069-3930-73 100 mg tablets (500 count package).  
NDC 0663-3930-41 100 mg tablets (100 [10 x 10] count package).  
NDC 0069-3930-41 100 mg tablets (unit dose).

S-060: NDC 0663-3940-66 250 mg tablets (100 count package).  
NDC 0663-3940-71 250 mg tablets (250 count package).  
NDC 0069-3940-71 250 mg tablets (250 count package).  
NDC 0663-3940-82 250 mg tablets (1000 count package).  
NDC 0063-3940-41 250 mg tablets (100 [10 x 10] ct package).  
NDC 0069-3940-41: 250 mg tablets (unit dose).

During an April 23, 2002, telephone conversation between myself and Mr. John Kennedy of Pfizer Inc, I cited a conversation held April 17, 2001 between Ms. Jena Weber of the Division and Mr. Craig Audet of Pfizer Inc.:

Mr. Kennedy confirmed that despite the April 17, 2001, conversation, the NDC numbers listed in the **HOW SUPPLIED** section of the final printed labeling submitted April 16, 2002 are the correct NDC numbers:

- NDC 0069-3930-66: 100 mg tablets, 100 count package
- NDC 0069-3940-66: 250 mg tablets, 100 count package
- NDC 0069-3940-82: 250 mg tablets, 1000 count package

[Note: Section 126 of Title I of the 1997 Food and Drug Administration Modernization Act amends section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353(b)(4)) to require, at a minimum, that the label of prescription products contain the symbol "Rx only." According to the FDA guidance entitled, *Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 - Elimination of Certain Labeling Requirements* (Issued 7/1998), the "Rx only" symbol is not required for package insert labeling, if located on the carton/container labeling. However, should a manufacturer choose to include the symbol, the Agency prefers that the symbol be located in the title section. The "Rx only" symbol for this package insert is located at the end of the HOW SUPPLIED section of the package insert, rather than at the beginning.]

#### Conclusions

Supplements-058 and -060 should be approved on the final printed labeling submitted April 16, 2002. The firm should be informed that the "Rx only" symbol should be relocated to the title section of the package insert. This can be implemented at the next printing and the Agency notified in the annual report.

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/s/

James Cross  
4/26/02 05:00:51 PM  
CSO

Food and Drug Administration  
Rockville, MD 20857

NDA 11-641/S-060

Pfizer Inc.  
Attention: Michelle G. Campbell, R.Ph.  
Director, Worldwide Regulatory Strategy  
235 E. 42nd St. 150/7/12  
New York, NY 10017

Dear Ms. Campbell:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diabinese (chlorpropamide) Tablets.

Your supplement, dated May 23, 2001, contains the following proposed revisions to the "Carcinogenesis, Mutagenesis, and Impairment of Fertility" subsection of the "Drug Interactions" section of the label:

1. Delete information from dog toxicity studies and replace with the following: "Studies with Diabinese have not been performed to evaluate carcinogenic or mutagenic potential."
2. Increase the upper dosing levels at which the suppression of spermatogenesis has been observed in rats.
3. Add information on the safety factor of Diabinese based on exposure in rat and dog versus human.

We also refer to our approvable letter dated June 29, 2001, notifying you that the supplement may be approved after submitting final printed labeling (FPL) revised as follows:

*Carcinogenesis, Mutagenesis, Impairment of Fertility:*

Studies with Diabinese have not been conducted to evaluate carcinogenic or mutagenic potential. Rats treated with continuous Diabinese therapy for 6 to 12 months showed varying degrees of suppression of spermatogenesis at a dose level of 250 mg/kg (5 times human dose based on body surface area). The extent of suppression seemed to follow that of growth retardation associated with chronic administration of high-dose Diabinese in rats. The human dose of chlorpropamide is 500 mg/day (300 mg/M<sup>2</sup>). Six and twelve month toxicity studies in the dog and rat, respectively, indicate 150 mg/kg is well tolerated. Therefore, the safety margins based upon body surface area comparisons are 3 times human exposure in the rat and 10 times human exposure in the dog.

CDER has an ongoing initiative to update labels to current standards when labeling supplements are submitted. Exposure comparisons between animal and human doses are no longer expressed on a mg/kg basis. Ideally, safety margins (exposure ratios) are calculated based upon actual plasma drug exposure data (AUC). For products without toxicokinetics data, safety margins are calculated based on mg/kg dose corrected for body surface area ( $\text{mg}/\text{M}^2$ ). This has been demonstrated to provide data that is more comparable to actual exposures because it corrects for differences in metabolic rate, etc.

The safety margins we cited are based on the following calculations:

Human dose =  $500 \text{ mg/day} \div 60 \text{ kg} = 8 \text{ mg/kg} \times 37 = 300 \text{ mg}/\text{M}^2$

NOAEL in rat =  $150 \text{ mg/kg} \times 6 = 900 \text{ mg}/\text{M}^2$  (3 times human  $\text{mg}/\text{M}^2$  dose)

NOAEL in dog =  $150 \text{ mg/kg} \times 20 = 3000 \text{ mg}/\text{M}^2$  (10 times human  $\text{mg}/\text{M}^2$  dose)

If you have any questions, call James T. Cross, Regulatory Project Manager, at 301-480-8174.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, M.D.

Director

Division of Metabolic and Endocrine Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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David Orloff  
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