

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 11-641/S-061

Trade Name: Diabinese Tablets

Generic Name: chlorpropamide

Sponsor: Pfizer Inc.

Approval Date: January 4, 2004

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NDA 11-641/S-061

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APPLICATION NUMBER:

NDA 11-641/S-061

APPROVAL LETTER



NDA 11-641/S-061

Pfizer Inc.
Attention: Marianne Kopelman
Director, Worldwide Regulatory Strategy
235 East 42nd Street
NY, NY 10017

Dear Ms. Kopelman:

Please refer to your supplemental new drug application dated December 17, 2002, received December 18, 2002, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Diabinese® (chlorpropamide) Tablets.

We acknowledge receipt of your submission dated December 30, 2002.

This "Special Supplement – Changes Being Effected" supplemental new drug application provides for the revision of the package insert to include post-marketing adverse reactions.

We completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on December 17, 2002. However, we have the following comments and requests for additional information. Written response is requested.

1. The **PRECAUTIONS, General, Hypoglycemia** section of the revised package insert states, "Renal and hepatic insufficiency may affect the disposition of DIABINESE . . .". Please provide justification for this statement.
2. The **PRECAUTIONS, General, Hypoglycemia** section of the revised package insert states, "Renal and 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." Both renal and hepatic insufficiency may diminish gluconeogenic capacity. We recommend you remove "the latter" from this statement at the next printing so that the statement would be as follows: "Renal and hepatic insufficiency may affect the disposition of DIABINESE and may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions."
3. Of note, Diabinese is misspelled a few times throughout the package insert.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
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.

We remind you that you must submit patent information on form FDA 3542, *Patent Information Submitted Upon and After Approval of an NDA or Supplement*, within 30 days of the date of this letter as required by 21 CFR 314.53(c)(2)(ii) and 314.53(d)(2) at the address provided by 21 CFR 314.53(d)(4). The form may be obtained at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>. To expedite review of this patent declaration form, we request you submit an additional copy of the form to the Center for Drug Evaluation and Research "Orange Book" staff at

Food and Drug Administration
Office of Generic Drugs, HFD-610
Orange Book Staff
7500 Standish Place
Metro Park North II
Rockville, MD 20855-2773

If you have any questions, please call Lina AlJuburi, Regulatory Project Manager, at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

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

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

/s/

David Orloff

1/4/04 04:25:45 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 11-641S-061

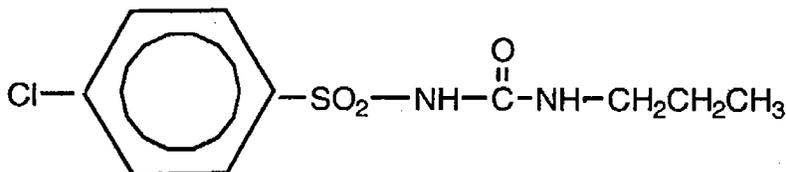
APPROVED LABELING

69-2141-00-5

DIABINESE®
(chlorpropamide)
TABLETS, USP
For Oral Use

DESCRIPTION

DIABINESE® (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/M²). 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 (21st 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).

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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-061

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE

Division of Metabolic and Endocrine Drug Products
REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 11-641/S-061

Name of Drug: Diabinese® (chlorpropamide) Tablets

Applicant: Pfizer Inc.

Material Reviewed:

Submission Date: December 17, 2002, Package Insert (PI), Final Printed Labeling (FPL)

Receipt Date: December 18, 2002

Amendment Submission Date: December 30, 2002, PI, FPL

Amendment Receipt Date: December 30, 2002

Background and Summary

Diabinese Tablets were approved October 28, 1958 for the indication of adjunct therapy to diet to lower blood glucose in patients with type 2 diabetes whose hyperglycemia cannot be controlled by diet alone.

S-061 was submitted as "Special Supplement – Changes Being Effectuated", under 21 CFR 314.70(c), to provide for the addition of post-marketing adverse reactions to the Contraindications, Precautions, Drug Interactions, and Adverse Reactions sections of the PI.

When the firm submitted the supplement, it was not clear if the supplement qualified for submission under this regulation since it was not clear if the labeling contained in the submission was FPL or not (the labeling contained an updated Identifier number and revision date, and with the advent of electronic submissions of labeling, FPL submissions often times do not have the same format as commercially used PIs). In addition, the firm had not submitted the required 20 copies. The firm was contacted, and they submitted sufficient copies of the labeling, bound on heavyweight paper, and the labeling was acknowledged and reviewed as a CBE supplement.

Review

The proposed PI (Identifier 69-2141-00-5, Revised August 2002) was compared to the currently approved PI (Identifier 69-2141-00-4, Revised October 2001, Approved May 16, 2002 with S-060). Of note, Diabinese was misspelled a few times throughout the package insert. The modifications are specifically as follows (underlined=additions, strikethrough=deletions):

CLINICAL PHARMACOLOGY

“DIABINESE exerts a hypoglycemic effect in / ~~in~~ healthy subjects within one hour, becoming maximal at 3 to 6 hours and persisting for at least 24 hours.”

Note: This is an acceptable editorial revision.

INDICATIONS AND USAGE

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

Note: This is an acceptable change in medical terminology.

CONTRAINDICATIONS

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

Note: These changes increase the safety measures and are found acceptable.

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 / ~~also~~ / affect the disposition of DIABINESE and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions.”

“*Loss of control of blood glucose:* . . . 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.”

Note: These changes were found acceptable by Dr. David Orloff on December 8, 2003.

LABORATORY TESTS

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

Note: These changes were found acceptable by Dr. Robert Misbin on December 5, 2003.

DRUG INTERACTIONS

The header **“The following products can lead to hypoglycemia:”** has been added.

Note: This is an acceptable editorial revision.

“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.”

Note: This text was already contained in the labeling, therefore, it is acceptable.

“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).”

Note: This text, except for the last sentence, was already contained in the labeling. This change was found acceptable by Dr. Robert Misbin on December 5, 2003.

The header **“The following products can lead to hyperglycemia”** has been added.

Note: This is an acceptable editorial revision.

Pregnancy

Teratogenic Effects:

“... DIABINESE should be given to a pregnant woman only if the potential benefits justify the potential risk to the patient and fetus.”

Note: This subsection has been revised to conform to the wording in 21 CFR 201.57 for drugs assigned to Pregnancy Category C.

“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.”

Note: This is an acceptable editorial revision.

Nonteratogenic Effects:

“... 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.”

“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.”

Note: These changes were found acceptable by Dr. Jeri El Hage on December 11, 2003.

ADVERSE REACTIONS

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

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

Note: These changes were found acceptable by Dr. Robert Misbin on December 5, 2003.

“Gastrointestinal”

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

Note: This statement was taken out of the *Gastrointestinal Reactions* subsection and placed under this new subsection. This is an acceptable editorial revision.

“Skin/Appendages: ...”

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

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

Note: These are acceptable editorial revisions.

DOSAGE AND ADMINISTRATION

Non-insulin-dependent diabetic was replaced with type 2 diabetes throughout this section.

Note: This is an acceptable editorial change.

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 also 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.

During the insulin withdrawal period, the patient should self-monitor glucose levels at least three times daily.

Note: These changes were found acceptable by Dr. Robert Misbin on December 5, 2003.

REFERENCES

1. USP: Drug Information for the Health Care Professional (21st Edition) 2001, pg 308.
2. Hansten PD and Horn 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).

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69-2141-00-5

Revised August 2002

Note: These are acceptable editorial additions and revisions.

Conclusions

An approval letter with comments and request for additional information in regard to the PRECAUTIONS section should be drafted for S-061. The comments are specifically as follows:

1. The **PRECAUTIONS, General, Hypoglycemia** section of the revised package insert states, "Renal and hepatic insufficiency may affect the disposition of DIABINESE . . .". Please provide justification for this statement.
2. The **PRECAUTIONS, General, Hypoglycemia** section of the revised package insert states, "Renal and 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." Both renal and hepatic insufficiency may diminish gluconeogenic capacity. We recommend you remove "the latter" from this statement at the next printing so that the statement would be as follows: "Renal and hepatic insufficiency may affect the disposition of DIABINESE and may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions."

3. Of note, Diabinese is misspelled a few times throughout the package insert.

This approved package insert contains the Identifier 69-2141-00-5 and an August 2002 revision date.

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
HFD-510

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

/s/

Lina Aljuburi
1/5/04 11:24:25 AM
CSO