DESCRIPTION

DIABINESE brand of chlorpropamide is available as 100 mg and 250 mg tablets. Inert ingredients present in DIABINESE tablets include: alginic acid, calcium carbonate, corn starch, FD & Blue No. 1, hydroxypropyl cellulose, magnesium stearate and sodium lauryl sulfate.

\[ \text{Chemical Structure of Chlorpropamide} \]

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties
DIABINESE is a potent, active, oral hypoglycemic agent indicated for the treatment of selected diabetic patients. It is generally used alone to control the mild to moderately severe non-insulin dependent diabetes mellitus. While DIABINESE is a sulfonamide derivative, it is devoid of antibacterial activity.

Mechanism of Action
DIABINESE brand of chlorpropamide is an oral hypoglycemic of the sulfonylurea class. The precise mechanism of action is not completely understood but it is not an oral insulin. Its mode of action is believed to be that of stimulation of synthesis and release of endogeneous insulin, an effect that is dependent on functioning beta cells in the pancreas. Extrapancreatic effects may plan a part in the mechanism of action of oral sulfonylureas.

There is no evidence that improvement in pancreatic beta cell function, with consequent improvement in glucose tolerance, may occur with prolonged administration of DIABINESE. Accordingly, in individuals with asymptomatic diabetes mellitus, principally manifested by an abnormal glucose tolerance, continuous use of DIABINESE may result in “normalization” of their tolerance to glucose.

The potency of DIABINESE is approximately six times that of tolbutamide. Some experimental results suggest that its increased effectiveness may be the results of slower excretion and absence of significant deactivation.
**Pharmacokinetic Properties**

**Pharmacokinetics**
DIABENESE 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 to 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.

DIABENESE exerts a hypoglycemic effect in normal humans within one hour, becoming maximal at 3 to 6 hours and persisting for at least 24 hours.

**Preclinical Safety Data**
Chronic toxicity studies have been carried out in dogs and rats. Dogs treated for 6, 13 or 20 months with doses of DIABENESE greater than 20 times the human dose, have not shown any gross histological or pathological abnormalities. After treatment with 100 mg/kg of DIABINESE for 20 months, a dog showed no histopathological liver changes. Rats treated with continuous DIABINESE therapy for 6 to 12 months showed varying degrees of suppression of spermatogenesis at higher dosage levels (up to 125 mg/kg). The extent of suppression seemed to follow that of growth retardation associated with chronic administration of high dose DIABINESE in rats.

**THERAPEUTIC INDICATION**
Chlorpropamide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

DIABENESE may also prove effective in controlling certain patients who have shown an inadequate response or true primary or secondary failure to other sulfonylurea agents. In patients requiring high doses or frequent administration of another oral hypoglycemic agent, control may be facilitated through its use.

*Concurrent Diabinese Biguanide Therapy*: The concurrent use of DIABINESE with a biguanide (phenformin, metformin) is indicated in the treatment of uncomplicated diabetes mellitus of the stable, nonketonic, NIDDM type that cannot be controlled by diet alone, by diet and insulin, or by diet and sulfonylurea agents. The appropriate biguanide product document should be consulted for complete details of patient selection, indications, warnings and dose.

**CONTRAINDICATIONS**
DIABINESE is contraindicated in patients with:

1. Known hypersensitivity to the drug.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
3. DIABINESE should not be used in insulin-dependent diabetes mellitus (IDDM, formerly
SPECIAL WARNINGS ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

G6PD-deficiency: Since chlorpropamide belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency. Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to haemolytic anemia and a non-sulfonylurea alternative should be considered.

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.

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 lone. 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 shown an increase in over-all mortality. Despite controversy regarding the interpretation of these results, the finding of the UGDP study provide an adequate basis for this warming. The patients should be informed of the potential risks an 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 warming may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

General

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Diabinese or any other oral anti-diabetic drug.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may cause elevated blood levels of DIABINESE and the latter may also diminish glyconeogenic 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 drugs is used.

Because of the long half life of DIABINESE, 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 decrease 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.

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

*Laboratory Tests*
Blood and urine glucose should be monitored periodically. Measurement of glycosilated hemoglobin may be useful.

*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 or regular testing of urine and/or 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.

**INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION**

The hypoglycemic action of sulfonylurea may be potentiated by certain drugs including nonsteroidal anti-inflammatory drugs and other agents 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.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroid, 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.
A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported with some sulfonylureas. Whether this interaction also occurs with intravenous, topical or vaginal preparations of miconazole is not known.

In some patients, a disulfiram-like reaction may be produced by ingestion of alcohol.

**Antifungals:**
Voriconazole: Although not studied, voriconazole may increase the plasma levels of sulfonylureas, (e.g. tolbutamide, glipizide, and glyburide) and therefore cause hypoglycemia. Careful monitoring of blood glucose is recommended during co-administration.

**Laboratory Tests**
DIABINESE does not interfere with the usual tests to detect albumin in the urine.

**Pregnancy and lactation**

*usage in Pregnancy*
Teratogenic Effects: Animal reproduction 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 clearly needed. Because recent information suggests 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.

*Usage in 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 women breast feed while taking this medication.

**Effect on ability to drive and operate machinery**
The effect of DIABINESE on the ability to drive or operate machinery has not been studies. However, there is no evidence to suggest that DIABINESE may affect these abilities.

**UNDESIRABLE EFFECTS**
The majority of side effects have been dose related, transient, and have responded to dose reduction or withdrawal of the medication. However, clinical experience thus far has shown that, as with other sulfonylureas, some side effects associated with hypersensitivity may be severe and deaths have been reported in some instances.
Hypoglycemia: See WARNINGS and PRECAUTIONS and OVERDOSAGE SECTIONS

Gastrointestinal Reactions: Cholestatic jaundice may occur rarely. DIABINESE should be discontinued if this occurs. 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. They tend to be dose related and may disappear when dosage is reduced.

Dermatologic Reactions: 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 DIABINESE; if skin reactions persist the drug should be discontinued.

Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

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

Hematologic reactions: leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic reactions: Hepatic porphyria and disulfiram-like reactions have rarely been reported with DIABINESE. See Interaction Section.

Endocrine reactions: on rare occasions, DIABINESE 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

Preclinical testing has determined the oral LD$_{50}$ in mice to be 1675 mg/kg, in dogs to be 800 mg/kg and in rats to be 2390 mg/kg.

Signs and Symptoms of Overdosage
Overdosage of sulfonylureas including DIABINESE can produce severe hypoglycemia. Severe hypoglycemia may cause coma, seizure or other neurological impairments, infrequently.

Treatment of Overdosage
Mild hypoglycemia 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.

**POSOLOGY AND METHOD OF ADMINISTRATION**

**Patients Selection**
The most likely patient for therapy is one in whom diabetes is of the NIDDM type, stable, and not controllable by dietary regulation alone. A past history of diabetic coma does not necessarily preclude successful therapeutic control with DIABINESE. A trial period may be indicated in certain patients who might be expected to respond to this type of medication, but who failed in initial trials with or after having been on other oral sulfonylurea agents, or in patients whose diabetic control on such agents has not been satisfactory DIABINESE may prove effective and provide improved control of the diabetes. The final evaluation of response in patients who qualify as candidates for DIABINESE is a therapeutic trial for a period of at least seven days.

During the trial period, the absence of ketonuria together with a satisfactory control, indicates that the patients is responsive and amenable to control with the drug. However, the development of ketonuria within 24 hours after withdrawal of insulin usually will be indicate of a poor response. The patients is considered nonresponsive if he fails to achieve satisfactory lowering of blood sugar levels or fails to obtain objective or subjective clinical improvement and if the develops ketonuria or glycosuria. Insulin is indicated for the therapy of such patients.

Some patients fail to respond initially (primary failure), or gradually lose their responsiveness to sulfonylurea drugs (secondary failure), including DIABINESE. Alternatively, DIABINESE may be effective in some patient who have not responded or have ceased to respond to other sulfonylureas.

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.

In initiating treatment for NIDDM, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patients. 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.

Use of DIABINESE must be viewed by both the physicians and patients as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restrain. Furthermore, loss of blood glucose control on diet alone may be transient, thus requiring only short term administration of DIABINESE.

**Dosage regimen**
There is no fixed dosage regimen for the management of diabetes mellitus with DIABINESE or other hypoglycemic agents. In addition to the usual monitoring of urinary glucose, 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 patients response to therapy.

Short term administration of DIABINESE may be sufficient during periods of transient loss of control in patients usually well controlled 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 PRIMARY DOSE IS NOT NECESSARY AND SHOULD NOT BE USED.

Initial Therapy
The mild to moderately severe, middle-aged, stable NIDDM patient should be started on 250 mg daily.

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

The large majority of mild to moderately severe middle-aged, stable NIDDM 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 percent reduction in insulin for the first few days, with subsequent further reductions dependent upon the response.

During the insulin withdrawal period, the patient should test his urine for sugar and ketone bodies at least three times daily and report the results frequently to his physician. If the results 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
During maintenance programs, DIABINESE should be discontinued if satisfactory lowering of blood glucose is not longer achieved. Judgments should be based on regular clinical and laboratory evaluations.

Most moderately, severe, middle-aged stable NIDDM patients are controlled by approximately 250 mg daily. Many investigators have found that some milder diabetics do well on daily doses of 100-125 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.

**Usage in Special Patients**
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 Warnings and precautions section). Because the geriatric diabetic patient appears to be more sensitive to the hypoglycemic effect of sulfonylurea drugs, older patients should be started on similar amounts of DIABINESE, in the range of 100 to 125 mg daily.

**Concurrent DIABINESE - Biguanide Therapy**
DIABINESE / Metformin dosage: The dosage of DIABINESE should be maintained at or increased to 500 mg. If control is still inadequate, metformin may be added at a dosage of 0.5 gram twice daily, increasing by 0.5 to 1.0 gram every one to two weeks to a maximum of 3 grams daily.
If adequate control is obtained without side effects, reduction in dosage of both DIABINESE and metformin should be undertaken slowly (reducing the dosage of one drug at a time) in an attempt to maintain control with the least possible medication.

**SUPPLY**

DIABINESE is available as:

100 mg tablets; box of 10 blisters @ 10 tablets
Reg. No. DKL 7219803810A1

250 mg tablets; box of 10 blisters @ 10 tablets
Reg. No. DKL 7219803810B1

STORE BELOW 30°C AT A DRY PLACE

HARUS DENGAN RESEP DOKTER

PRESCRIPTION ONLY

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