CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074619

Trade Name : GLIPIZIDE TABLETS USP

Generic Name: Glipizide Tablets USP 5mg and 10mg

Sponsor : Sidmak Laboratories Inc.

Approval Date: April 4, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074619

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074619

APPROVAL LETTER

ANDA 74-619

APR 4 1997

Sidmak Laboratories, Inc.
Attention: Jairaj Mehta
17 West Street
P.O. Box 371
East Hanover, NJ 07936

Dear Sir:

This is in reference to your abbreviated new drug application dated Februay 6, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Glipizide Tablets USP, 5 mg and 10 mg.

Reference is also made to your amendments dated September 5, 1995; May 7, and 10, 1996; and March 17, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Glipizide Tablets USP, 5 mg and 10 mg to be bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Glucotrol® Tablets, 5 mg and 10 mg, respectively, of Pfizer, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of these drugs.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

[redacted] 4/4/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-619
Division File
FIELD COPY
HFD-600/Reading File
HFD-92
HFD-610/JPhillips
HFD-210/B.Poole

Endorsements:

HFD-625/MShaikh/3/19/97 [redacted] 3/25/97
HFD-625/MSmela/3/20/97 pending EER update
HFD-620/ARudman/ 3/25/97
HFD-617/S O'Keefe/PM/3/2
HFD-613/JGrace/3/21/97
HFD-613/CHolquist/3/21/97
F/t by: gp/3/25/97
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F/T by: gp/3/25/97
APPROVED

[redacted] 3/26/97

Sat. checkers, pending acceptable EER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074619

FINAL PRINTED LABELING

mar 80

NDC 50111-584-01

Glipizide Tablets, USP

5 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Sidmak. LABORATORIES, INC.

1997

EACH TABLET CONTAINS:
Glipizide, USP ..... 5 mg
Dispense in a tight container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.
Control No.:
Exp. Date:
Iss. 8/95

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

3 50111-584-01 3

NDC 50111-584-01

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SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

3 50111-584-01 3

NDC 50111-584-02

Glipizide Tablets, USP

5 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Sidmak. LABORATORIES, INC.

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Glipizide, USP..... 5 mg

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USUAL DOSAGE: See package insert.

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Exp. Date:
Iss. 8/95

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

0 50111-584-02 3

NDC 50111-584-02

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SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

0 50111-584-02 3

NDC 50111-585-01

Glipizide Tablets, USP

10 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Sidmak. LABORATORIES, INC.

EACH TABLET CONTAINS:
Glipizide, USP ..... 10 mg
Dispense in a tight container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.

Control No.:
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SIDMAK LABORATORIES, INC.
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SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

N 3 50111-585-02 7

abnormalities to glipizide is uncertain, and they have rarely been associated with clinical symptoms.

OVERDOSAGE: There is no well documented experience with glipizide overdosage. The acute oral toxicity was extremely low in all species tested (LD_{50} greater than 4 g/kg).

Overdosage of sulfonylureas including glipizide 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. Clearance of glipizide from plasma would be prolonged in persons with liver disease. Because of the extensive protein binding of glipizide, dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION: There is no fixed dosage regimen for the management of diabetes mellitus with glipizide or any other hypoglycemic agent. 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 patient's response to therapy.

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

In general, glipizide should be given approximately 30 minutes before a meal to achieve the greatest reduction in postprandial hyperglycemia.

Initial Dose: The recommended starting dose is 5 mg, given before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg.

Titration: Dosage adjustments should ordinarily be in increments of 2.5 to 5 mg, as determined by blood glucose response. At least several days should elapse between titration steps. If response to a single dose is not satisfactory, dividing that dose may prove effective. The maximum recommended once daily dose is 15 mg. Doses above 15 mg should ordinarily be divided and given before meals of adequate caloric content. The maximum recommended total daily dose is 40 mg.

Maintenance: Some patients may be effectively controlled on a once-a-day regimen, while others show better response with divided dosing. Total daily doses above 15 mg should ordinarily be divided. Total daily doses above 30 mg have been safely given on a b.i.d. basis to long-term 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 **PRECAUTIONS** section).

Patients Receiving Insulin: As with other sulfonylurea-class hypoglycemics, many stable non-insulin-dependent diabetic patients receiving insulin may be safely placed on glipizide. When transferring patients from insulin to glipizide, the following general guidelines should be considered:

For patients whose daily insulin requirement is 20 units or less, insulin may be discontinued and glipizide therapy may begin at usual dosages. Several days should elapse between glipizide titration steps.

For patients whose daily insulin requirement is greater than 20 units, the insulin dose should be reduced by 50% and glipizide therapy may begin at usual dosages. Subsequent reductions in insulin dosage should depend on individual patient response. Several days should elapse between glipizide titration steps.

During the insulin withdrawal period, the patient should test urine samples for sugar and ketone bodies at least three times daily. Patients should be instructed to contact the prescriber immediately if these tests are abnormal. In some cases, especially when the patient has been receiving greater than 40 units of insulin daily, it may be advisable to consider hospitalization during the transition period.

Patients Receiving Other Oral Hypoglycemic Agents: As with other sulfonylurea-class hypoglycemics, no transition period is necessary when transferring patients to glipizide. Patients should be observed carefully (1 to 2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (e.g., chlorpropamide) to glipizide due to potential overlapping of drug effect.

HOW SUPPLIED: Glipizide Tablets, USP:

5 mg - White, round, bisected tablets in bottles of 100 and 500.
Debossed: SL 584

10 mg - White, round, bisected tablets in bottles of 100 and 500.
Debossed: SL 585

Dispense in a tight container defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

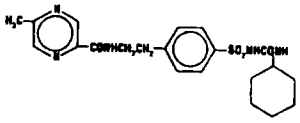
Manufactured by
SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

P08-0584

Iss 8/95

Description: Glipizide is an oral blood-glucose-lowering drug of the sulfonylurea class.

The Chemical Abstracts name of glipizide is 1-cyclohexyl-3-{[p-[2-(5-methylpyrazinecarboxamido)ethyl]-phenyl]sulfonyl}urea. The molecular formula is $C_{21}H_{27}N_5O_4S$; the molecular weight is 445.55; the structural formula is shown below:



Glipizide is a whitish, odorless powder with a pKa of 5.9. It is insoluble in water and alcohols, but soluble in 0.1 *N* NaOH; it is freely soluble in dimethylformamide.

Each tablet, for oral administration, contains 5 mg or 10 mg of glipizide. Tablets also contain colloidal silicon dioxide, corn starch, anhydrous lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch and sodium starch glycolate.

P08-0584

GLIPIZIDE TABLETS, USP

Iss. 8/95

CLINICAL PHARMACOLOGY: Mechanism of Action: The primary mode of action of glipizide in experimental animals appears to be the stimulation of insulin secretion from the beta cells of pancreatic islet tissue and is thus dependent on functioning beta cells in the pancreatic islets. In humans glipizide 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 glipizide lowers blood glucose during long-term administration has not been clearly established. In man, stimulation of insulin secretion by glipizide in response to a meal is undoubtedly of major importance. Fasting insulin levels are not elevated even on long-term glipizide administration, but the postprandial insulin response continues to be enhanced after at least 6 months of treatment. The insulinotropic response to a meal occurs within 30 minutes after an oral dose of glipizide in diabetic patients, but elevated insulin levels do not persist beyond the time of the meal challenge. Extrapancreatic effects may play a part in the mechanism of action of oral sulfonylurea hypoglycemic drugs.

Blood sugar control persists in some patients for up to 24 hours after a single dose of glipizide, even though plasma levels have declined to a small fraction of peak levels by that time (see **Pharmacokinetics** below).

Some patients fail to respond initially, or gradually lose their responsiveness to sulfonylurea drugs, including glipizide. Alternatively, glipizide may be effective in some patients who have not responded or have ceased to respond to other sulfonylureas.

Other Effects: It has been shown that glipizide therapy was effective in controlling blood sugar without deleterious changes in the plasma lipoprotein profiles of patients treated for NIDDM.

In a placebo-controlled, crossover study in normal volunteers, glipizide had no antidiuretic activity, and, in fact, led to a slight increase in free water clearance.

Pharmacokinetics: Gastrointestinal absorption of glipizide in man is uniform, rapid, and essentially complete. Peak plasma concentrations occur 1 to 3 hours after a single oral dose. The half-life of elimination ranges from 2 to 4 hours in normal subjects, whether given intravenously or orally. The metabolic and excretory patterns are similar with the two routes of administration, indicating that first-pass metabolism is not significant. Glipizide does not accumulate in plasma on repeated oral administration. It has been reported that total absorption and disposition of an oral dose was unaffected by food in normal volunteers, but absorption was delayed by about 40 minutes. Thus glipizide was more effective when administered about 30 minutes before, rather than with, a test meal in diabetic patients. Protein binding was studied in serum from volunteers who received either oral or intravenous glipizide and found to be 98-99% one hour after either route of administration. The apparent volume of distribution of glipizide after intravenous administration was 11 liters, indicative of localization within the extracellular fluid compartment. In mice no glipizide or metabolites were detectable autoradiographically in the brain or spinal cord of males or females, nor in the fetuses of pregnant females. In another study, however, very small amounts of radioactivity were detected in the fetuses of rats given labelled drug.

The metabolism of glipizide is extensive and occurs mainly in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Less than 10% unchanged glipizide is found in the urine.

INDICATIONS AND USAGE: Glipizide tablets are indicated as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with non-insulin-dependent diabetes mellitus (NIDDM; type II), formerly known as maturity-onset diabetes, after an adequate trial of dietary therapy has proved unsatisfactory.

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 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 glipizide 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 also may be transient, thus requiring only short-term administration of glipizide.

During maintenance programs, glipizide 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 glipizide 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: Glipizide 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.

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 2 1/2 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 overall 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 glipizide 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: ***Renal and Hepatic Disease:*** The metabolism and excretion of glipizide may be slowed in patients with impaired renal and/or hepatic function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted.

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 glipizide 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.

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 glipizide and administer insulin.

The effectiveness of any oral hypoglycemic drug, including glipizide, 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.

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

Information for Patients: Patients should be informed of the potential risks and advantages of glipizide and of alternative modes of therapy. They should also be informed about the importance of adhering to dietary instructions, of a regular exercise program, and of 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.

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents, some azoles, 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 glipizide, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving glipizide, the patient should be observed closely for loss of control. *In vitro* binding studies with human serum proteins indicate that glipizide binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to the clinical situation and in the use of glipizide with these drugs.

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 glipizide, the patient should be closely observed for loss of control. When such drugs are withdrawn from a patient receiving glipizide, 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. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. The effect of concomitant administration of fluconazole and glipizide was reported in a placebo-controlled crossover study in normal volunteers. All subjects received glipizide alone and following treatment with 100 mg of fluconazole as a single daily oral dose for 7 days. The mean percentage increase in the glipizide AUC after fluconazole administration was 56.9% (range: 35 to 81).

Carcinogenesis, Mutagenesis, Impairment of Fertility: A twenty month study in rats and an eighteen month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C: Glipizide was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of glipizide. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well-controlled studies in pregnant women. Glipizide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 glipizide is used during pregnancy, it should be discontinued at least one month before the expected delivery date.

Nursing Mothers: Although it is not known whether glipizide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If the drug is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS: In U.S. and foreign controlled studies, the frequency of serious adverse reactions reported was very low. Of 702 patients, 11.8% reported adverse reactions and in only 1.5% was glipizide discontinued.

Hypoglycemia: See **PRECAUTIONS** and **OVERDOSAGE** sections.

Gastrointestinal: Gastrointestinal disturbances are the most common reactions. Gastrointestinal complaints were reported with the following approximate incidence: nausea and diarrhea, one in seventy; constipation and gastralgia, one in one hundred. They appear to be dose-related and may disappear on division or reduction of dosage. Cholestatic jaundice may occur rarely with sulfonylureas; glipizide should be discontinued if this occurs.

Dermatologic: Allergic skin reactions including erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about one in seventy patients. These may be transient and may disappear despite continued use of glipizide; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

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

Metabolic: Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas. In the mouse, glipizide pretreatment did not cause an accumulation of acetaldehyde after ethanol administration. Clinical experience to date has shown that glipizide has an extremely low incidence of disulfiram-like alcohol reactions.

Endocrine Reactions: Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with this and other sulfonylureas.

Miscellaneous: Dizziness, drowsiness, and headache have each been reported in about one in fifty patients treated with glipizide. They are usually transient and seldom require discontinuance of therapy.

Laboratory Tests: The pattern of laboratory test abnormalities observed with glipizide was similar to that for other sulfonylureas. Occasional mild to moderate elevations of SGOT, LDH, alkaline phosphatase, BUN and creatinine were noted. One case of jaundice was reported. The relationship of these

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074619

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 74-619

3. NAME AND ADDRESS OF APPLICANT
Sidmak Laboratories, Inc.
17 West Street., P. O. Box 371
East Hanover, NJ 07936

4. BASIS OF SUBMISSION
Acceptable per CR # 1 completed by this reviewer.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Glipizide Tablets, 5 mg & 10 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original Submission: 2-6-95
Accepted for filing: 2-7-95 (letter date 3-8-95)
NC (Bio): 9-5-95.
Major amendment: 10-9-95 (Response to NA letter dated 6-12-95)
5-7-96 Biodata
5-10-96 Biodata
Major Amendment: 1-15-97 (response to 2-22-96 letter) [resubmitted on 1-15-97 as 8-27-96 submission failed to reach OGD's Doc. Room]
* Minor Amendment: 3-17-97 (Response to 3-5-97 NA letter)

FDA:
NA letter (Chemistry + Labeling): 6-19-95
NA letter (Bioequivalency): 12-6-95
NA letter (Chemistry + Labeling): 2-22-96
Bio Acceptance Letter: 11-25-96
NA letter: 3-5-97

10. PHARMACOLOGICAL CATEGORY
Hypoglycemic Agent

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
[redacted]

[redacted]

DOSAGE FORM
Tablets

14. POTENCY
5 mg & 10 mg

15. CHEMICAL NAME AND STRUCTURE
Listed in proposed labeling insert per Supplement # 8 to USP XXII.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
1. [redacted] manufacturer of BDS remains satisfactory per M. Shaikh's review completed on 2-2-96.
2. EER became acceptable on 12-7-95. Based on current OGD's policy regarding EER, a new EER has been submitted on 2-20-97 for an update.
3. FPL became acceptable on 2-1-96. Remains acceptable per note made by C. Holquist on CR # 3.
4. Bio status became acceptable per bio acceptability letter to the firm issued on 11-25-96.
5. USP method verification report completed by PHI-DO for Glipizide Tablets USP, 10 mg became acceptable.

CONCLUSIONS AND RECOMMENDATIONS
Approved pending acceptable EER update.

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
3-19-97

cc: ANDA 74-619
Division File
Field Copy

Endorsements:

HFD-625/M.Shaikh/3/19/97 [redacted] 3/26/97
HFD-625/M.Smela/3/20/97
x:\new\firmsnz\sidmak\ltrs&rev\74619rev.4
F/t by: gp/3/25/97

[redacted] 3/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074619

BIOEQUIVALENCE REVIEW(S)

ANDA 74-619

Sidmak Laboratories Inc.
Attention: Arun D. Kulkarni
17 West Street
P.O. BOX 371
East Hanover NJ 07936

NOV 25 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Glipizide Tablets USP, 5 mg and 10 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23-NF 18, Supplement 1.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

[redacted]

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NOV 8 1996

Glipizide
5 mg and 10 mg Tablets
ANDA #74-619
Reviewer: Z.Z. Wahba
wp#74619sf.596

Sidmak Laboratories, Inc
E. Hanover, N.J.
Submission Date:
May 07, 1996
May 10, 1996

RESPONSES TO THE DEFICIENCIES THAT WERE IDENTIFIED IN THE IN VIVO BIOEQUIVALENCE STUDY UNDER FASTING CONDITIONS AND IN VITRO DISSOLUTION TESTING DATA

AND

REVIEW OF IN VIVO BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS

I. Amendment to a Reviewed In Vivo Bioequivalence Study Under Fasting Conditions

BACKGROUND

The firm has previously submitted an in vivo bioequivalence study (single dose) under fasting conditions comparing its 10 mg strength Glipizide Tablets to the reference listed product, Pfizer's Glucotrol® Tablets 10 mg.

The submission was reviewed and was found incomplete by the Division of Bioequivalence (review dated November 22, 1995, ANDA #74-619) due to deficiency comments.

In this submission, the firm has responded to the deficiency comments and included additional information in the current submission.

Comment #1

Limited Food Effect Study:

Since glipizide is indicated as an adjunct to diet for the control of hyperglycemia, a food study is required to examine the effect of food on the tested drug product.

The firm should conduct a single-dose post-prandial bioequivalence study comparing equal doses of the test and reference products. The study should be conducted in a random, three-treatment (Treatments 1&2: the test and reference products should be dosed immediately after standard breakfast, Treatment 3: the test product should be dosed under fasting conditions), three-period, cross-over design using a sufficient number of healthy subjects. A wash-out period should be at least two week between periods 1, 2, and 3 dosing.

Response to Comment #1

The firm has submitted a non-fasting study which is included in this report. The non-fasting study was reviewed and found acceptable (see the part "review of in vivo bioequivalence study under non-fasting conditions" of this report).

The firm's response to comment #1 is acceptable.

THE FOLLOWING RESPONSES PERTAIN TO DEFICIENCIES WITH REGARD TO THE SINGLE DOSE FASTING STUDY AND DISSOLUTION TESTING DATA:

Comment #2

Information on the batch/lot size for the test product, the assay potency and content uniformity data for both the test and reference products, in addition to the date of manufacturing the test product should be included.

Response to Comment #2

For the test product:

Batch size [redacted]tablets
Assay Potency 102.0%
Content Uniformity 102.1%
Manufacturing date 9/23/1993

For the reference product:

Assay Potency 102.5%
Content Uniformity 102.8%

The firm's response to comment #2 is acceptable.

Comment #3

A detailed description of the dissolution methodology (including type of equipments that were used) should be provided. In addition, the dates which dissolution analysis were performed should be provided. It should be noticed that the Division of Bioequivalence considers the current USP methodology to be the regulatory method which must be used for dissolution comparison.

Response to Comment #3

The firm has submitted the information needed (vol. #c2.1, Item #2). The assay methodology was [redacted] The dissolution data was reviewed and found acceptable (see the part "review of in vivo bioequivalence study under fasting conditions" of this ANDA).

The firm's response to comment #3 is acceptable.

Comment #4

The following items are missing from the submission:

a. The raw data of subjects blood glucose levels

b. Table #T4.1
c. Intraday assay validation data.

Response to Comment #4

The firm has submitted the missing items (vol. #c2.1, items #3, 4 and 5).

The firm's response to comment #4 is acceptable.

Comment #5

5. [redacted]

Response to Comment #5

[redacted]

The firm's response to comment #5 is acceptable.

II. REVIEW OF IN VIVO BIOEQUIVALENCE STUDY Under NON-FASTING CONDITIONS (Clinical Study #930015)

I. OBJECTIVE:
To review:

Sidmak's in vivo bioequivalence studies under non-fasting conditions comparing its 10 mg strength Glipizide Tablets to the reference listed product, Pfizer's Glucotrol® Tablets 10 mg.

II. BACKGROUND:

Glipizide is a sulfonylurea antidiabetic agent. It is used to lower blood glucose concentration in diabetic and non-diabetic individuals. The precise mechanism(s) of sulfonylurea antidiabetic agents has not been clearly established, but the drugs, including glipizide, initially appear to lower blood glucose concentration principally by stimulating secretion of endogenous insulin from beta cells of the pancreas.

Glipizide appears in the plasma or serum within 15-30 minutes and has average peak plasma or serum concentrations of approximately 310-450 ng/mL. Glipizide plasma concentrations occur 1-3 hours (with a range 1-6 hours) after a single oral dose. Food delays the absorption of the drug but does not affect peak serum concentrations achieved or the extent of absorption. The half life of elimination ranges from 2-4 hours in normal subjects, whether given intravenously or orally. Plasma glipizide levels of 20-90 ng/mL have been reported to be therapeutically effective. The drug does not accumulate in plasma on repeated oral administration. The metabolism of glipizide is extensive and occurs mainly in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Less than 10% unchanged glipizide is found in the urine.

Glipizide is indicated as an adjunct to diet for the control of hyperglycemia. Glipizide is commercially available as tablets of 5 mg or 10 mg, Glucotrol®, manufactured by Pfizer Inc.

A. Sponsor:
Sidmak Laboratories
17 West Street,
East Hanover, N.J. 07936

Study site
Clinical/Analytical Facilities
[redacted]

[redacted]

Dates of Sample Collection:
Period I: 01/05/1996 and 01/06/1996
Period II: 01/19/1996 and 01/20/1996
Period III: 02/02/1996 and 02/03/1996

Date of First Sample Analysis:
02/04/1996

Date of Last Sample Analysis:
02/09/1996

B. Study design:
Randomized, three-way single dose crossover study, under non-fasting conditions.

C. Subjects:
Eighteen (18) healthy male subjects were enrolled and 17 subjects completed the clinical study. Subject #15 elected to withdraw from the study after period I dosing. The subjects were in the range of 19 to 45 years of age, and their body weights were within ± 10% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

Subject Selection Criteria:
Only medically healthy subjects as determined by normal history, physical examination, laboratory profiles and EKG were enrolled in the study.

Subject Exclusion Criteria:
Subjects were excluded from the study based on the following criteria:

1. History of cardiovascular, pulmonary, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, hematological, hepatic, renal, psychiatric disease.
2. History of diabetes mellitus or complications (diabetic ketoacidosis).
3. Hypersensitivity to glipizide or other sulfonylurea-type drugs.
4. History of alcohol or drug abuse within the last year prior to the beginning of the study.
5. Any subject on an abnormal diet during the 4 weeks preceding the study.
6. A history of chronic alcohol or drug addiction.

7. Use of tobacco in any form.
8. Blood donation within the past 14 days (if the amount exceeded 500 mL), or 3 months (if the amount exceeded 750 mL) or 6 months (if amount exceeded 100 mL) or one year (if amount exceeded 2000 mL) of the study.
9. Receiving any investigational drug within 28 days prior to period I dosing.

Subject Restrictions:
1. No subject took any medications, including OTC products for at least 7 days prior to the beginning of the study until completion of the study.
2. No alcohol, xanthine and caffeine containing foods and beverages were allowed, beginning 24 hours prior to dosing until completion of the study.

D. Treatment Plan:

Treatment A:

1 X 10 mg Sidmak's Glipizide Tablet, Lot #93-023T, Batch size [redacted]tablets, assay potency 102.0%, content uniformity 102.1%, under fasting conditions.

Treatment B:

1 X 10 mg Sidmak's Glipizide Tablet, Lot #93-023T, Batch size [redacted]ablets, assay potency 102.0%, content uniformity 102.1%, under non-fasting conditions.

Treatment C:

1 X 10 mg Pfizer's Glucotrol® Tablet, Lot #28P009A, assay potency 102,5%, content uniformity 102.8%, expiration date: 8/1997, under non-fasting conditions.

Washout period: 14 days between doses.
A single 10 mg dose was given in each period of the study.

E. Drug, Food and Fluid Intake:

Subjects who received treatment A, fasted overnight (10 hours) before dosing and for 4 hours after each drug administration. Subjects who received treatments B and C, fasted overnight for 10 hours before they were fed a standard high fat breakfast, which was consumed in its entirety 30 minutes before drug administration. The standard breakfast consisted of one buttered English muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, 120 g hashed brown potatoes, 240 ml of whole milk and 180 ml of orange juice. Each dose was administered with 240 mL of 20% dextrose (D-glucose) solution in water at ambient temperature. In order to offset hypoglycemic effects, a 60 mL of sugar solution was administered at the following times after dosing: 0.25, 0.5, 0.75, 1, 1.25, 1.25, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75 and 4 hours. In addition, 20% D-glucose solution in

water was given to any subject who exhibited symptoms of hypoglycemia. Standard meals were provided at appropriate times thereafter (lunch at 4 hours post-dose, supper at 9 hours post-dose).

F. Assay Methodology:

[redacted]

[redacted]

G. <u>Blood sampling</u>:

Blood samples (10 mL each) were collected in Vacutainers containing EDTA at 0.0, 0.5, 1.0, 1.50, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10, 12, 16, 24 and 36 hours post-dosing. The plasma samples were separated, collected and promptly stored frozen at -22 °C until analysis.

H. **Adverse Events**:

The adverse reactions have been reported (ANDA #74619, vol. C2.1, section "Clinical Report") by the subjects with a possibility of linkage to the test or reference drug product. Examples for the adverse events were tiredness, headach, feeling dizzy, feeling shaky, lightheeaded, low blood glucose, runny nose. The adverse reactions were considered mild to moderate and no medication was given. No subject was discontinued from the study due to an adverse reaction.

I. **Data Analysis**:

Eighteen (18) healthy male subjects were enrolled and 17 subjects completed the clinical study. Subject #15 elected to withdraw from the study after period I dosing. The data set used for statistical analysis contained data from 17 subjects (subjects #1-14, 16 and 17). The firm mentioned in the submission (vol. C2.1, 'The Summary Section' page 2) that subject #9 vomited 4 hours post-dose (formula B) in Period 1 and the statistical analysis was performed with this subject excluded for formulation B. The reviewer reran the entire raw data (include subject #17) using SAS GLM system. The out come of the analysis of the plasma glipizide concentrations, and the pharmacokinetic parameters, AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and $T_{1/2}$ for the 17 subjects are presented as follow:

Table 4
Mean Plasma Concentrations of Glipizide in 17 Subjects Under Non-Fasting Conditions
Unit: ng/mL

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.00	0.00	0.00	0.00	0.00	0.00
0.5	56.84	82.66	24.16	70.69	6.47	12.92
1	115.65	176.07	161.32	213.03	165.44	210.80
1.5	105.94	98.18	316.64	283.27	310.09	270.71
2	158.82	199.83	382.26	237.64	368.24	245.17
2.5	184.14	183.33	427.76	208.53	391.92	215.89
3	249.78	234.88	442.21	168.20	423.02	190.38
3.5	303.76	217.99	440.84	140.67	431.32	118.51
4	342.24	211.38	447.79	156.43	446.62	96.86
5	477.38	171.63	410.11	126.23	443.25	120.51
6	509.03	136.83	367.71	138.05	403.90	134.00
8	342.99	142.54	251.45	94.18	302.98	153.25
10	209.75	107.34	184.91	106.03	196.95	122.65
12	141.52	79.69	127.83	89.01	127.08	93.81
16	72.01	49.28	70.29	80.41	66.02	62.81
24	20.87	25.78	25.61	57.27	17.28	27.64
36	0.00	0.00	1.46	6.04	0.00	0.00

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
0.5	2.35	8.78	3.73
1	0.72	0.70	0.98
1.5	0.33	0.34	1.02
2	0.42	0.43	1.04
2.5	0.43	0.47	1.09
3	0.56	0.59	1.05
3.5	0.69	0.70	1.02
4	0.76	0.77	1.00
5	1.16	1.08	0.93
6	1.38	1.26	0.91
8	1.36	1.13	0.83
10	1.13	1.06	0.94
12	1.11	1.11	1.01
16	1.02	1.09	1.06
24	0.81	1.21	1.48
36	0.00	.	.

MEAN1=Test-fast MEAN2=Test-Fed MEAN3=Ref.-Fed
RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 5
Pharmacokinetic Parameters of Glipizide (Arithmetic Means) in 17 Subjects Following a Single-Dose of 10 mg Glipizide Tablet under Non-Fasting Conditions

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
AUCI	4291.00	1371.44	4388.76	1480.25	4416.41	1465.73
AUCT	4064.00	1225.67	4176.82	1386.58	4207.59	1287.50
CMAX	638.29	120.50	600.74	122.17	611.40	111.79
KE	0.18	0.05	0.20	0.06	0.20	0.06
*LAUCI	4114.47	0.29	4189.34	0.31	4232.35	0.29
*LAUCT	3910.19	0.28	3993.94	0.30	4053.21	0.27
*LCMAX	627.50	0.19	588.23	0.22	601.72	0.19
THALF	4.02	1.06	3.78	1.19	3.69	1.19
TMAX	4.91	1.48	3.79	2.39	3.76	1.90

(CONTINUED)

PARAMETER	RMEAN12	RMEAN13	RMEAN23
AUCI	0.98	0.97	0.99
AUCT	0.97	0.97	0.99
CMAX	1.06	1.04	0.98
KE	0.92	0.90	0.98
*LAUCI	0.98	0.97	0.99
*LAUCT	0.98	0.96	0.99
*LCMAX	1.07	1.04	0.98
THALF	1.06	1.09	1.02
TMAX	1.29	1.30	1.01

MEAN1= Test-Fast MEAN2= Test-Fed MEAN3= Ref.-Fed
RMEAN23=T/R ratios (under non-fasting conditions)
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

Table 6
LSMEANS Pharmacokinetic Parameters Glipizide in 17 Subjects Following a Single-Dose of 10 mg Glipizide Tablet under Non-Fasting Conditions

PARAMETER	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
AUCI	4467.34	4576.97	4603.52	0.98	0.97	0.99
AUCT	4218.70	4344.55	4372.66	0.97	0.96	0.99
CMAX	645.89	605.80	618.90	1.07	1.04	0.98
*LAUCI	4249.37	4337.36	4379.28	0.98	0.97	0.99
*LAUCT	4030.02	4127.71	4185.59	0.98	0.96	0.99
*LCMAX	634.34	592.44	608.44	1.07	1.04	0.97

LSM1=LSMEAN Test-Fast LSM2=LSMEAN Test-Fed
LSM3=LSMEAN Ref.-Fed
RLSM23=T/R ratios (under non-fasting conditions)
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the antilog of the means of the logs.

1. Under non-fasting conditions, the mean plasma levels for glipizide reached the maximum around 4.0 hours (Table #4 and Figures #1 and 2).

2. The AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for the test product under non-fasting conditions were comparable to those for the reference product under the same conditions.

3. Under non-fasting conditions, the T/R mean ratios of the LSMEANS (Table #6) as well as geometric means (Table #5) for log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within the acceptable range of 0.8 to 1.2 that has been set by the Division of Bioequivalence.

4. The average mean values of the parameters T_{max}, $T_{1/2}$ and K_{el} for the test product were comparable to that of the reference product under non-fasting conditions.

5. Comment on the effect of food: The rate of absorption under non-fasting conditions was higher (up to 4.0 hours) as compared to the rate of absorption under fasting conditions. The mean T_{max} for the test product under non-fasting conditions was 3.79 hours while under fasting conditions was 4.91 hours. The AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for the test and reference products under non-fasting conditions were comparable to those for the test product under the fasting conditions.

III. COMMENTS:

1. Under fasting conditions: The firm's in vivo bioequivalence study under fasting conditions demonstrated that the test product, Sidmak's Glipizide Tablets 10 mg and the reference product, Pfizer's Glucotrol® Tablets 10 mg are bioequivalent. The 90% confidence intervals for the log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were all within the acceptable range of 80-125% (ANDA #74-619; submission date 02/06/1996; signed on 11/22/1995).

2. Under non-fasting conditions: The in vivo bioequivalence study under non-fasting conditions demonstrated that the test product, Sidmak's Glipizide Tablets 10 mg is bioequivalent to the reference product, Pfizer's Glucotrol® Tablets 10 mg. The ratios of the test mean to the reference mean for the AUC_{0-t}, $AUC_{0-\infty}$, C_{max} were within the acceptable range of 0.8 to 1.2.

3. Formulations Comparison: The firm has provided comparative formulations showing that 5 mg strength tablets are proportionally similar in their active and inactive ingredients to the 10 mg strength.

4. Dissolution Data: The firm has provided comparative dissolution data for its drug product, Glipizide Tablets, 10 mg and 5 mg, and the reference product, Pfizer's Glucotrol® Tablets 10 mg and 5 mg. The dissolution data for the test products are acceptable.

IV. RECOMMENDATIONS:

1. The two in vivo bioequivalence studies conducted by Simak Laboratories, Inc under fasting (ANDA #74-619; submission date 02/06/1996; signed on 11/22/1995; review by Z. Wahba, Ph.D.) and non-fasting (present review) conditions on its drug product, Simak's Glipizide Tablets, 10 mg (Lot #93-023T), comparing it to the reference drug product, Pfizer's Glucotrol® Tablets 10 mg (Lot #28P009A) have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Sidmak's Glipizide Tablets 10 mg is bioequivalent to the reference product, Pfizer's Glucotrol® Tablets 10 mg under fastind and non-fasting conditions.

2. The dissolution testing data conducted by Simak on its drug product, Glipizide Tablets, 10 mg (Lot #93-023T) and 5 mg strength (lot #93-025T) have been found acceptable. The firm's formulations for 5 mg strength is proportionally similar to the 10 mg strength tablets of the test product which underwent an acceptable bioequivalence study. The waiver of the in vivo bioequivalence study requirements for

the 5 mg strength of the test product is granted. From the Bioequivalence point of view, the Division of Bioequivalence deems the 5 mg strength of the test product to be bioequivalent to the reference product, Pfizer's Glucotrol® Tablets 5 mg.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml stimulated intestinal fluid without enzyme pH 7.5 at 37°C applying USP 23 Apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than [redacted] of the labeled amount of the drug product in the tablet is dissolved in 45 minutes.

The firm should be informed of the recommendations.

[redacted]

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE [redacted] for RM Oct 30, 1996
FT INITIALED RMHATRE

Concur: [redacted] Date: 11/8/96
Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA #74-619, (original, duplicate), HFD-630 (OGD), HFD-600 (Hare), HFD-658 (Mhatre, Wahba), Drug File, Division File
ZZWahba/101796/wp#74619sf.596

ANDA # 74-619

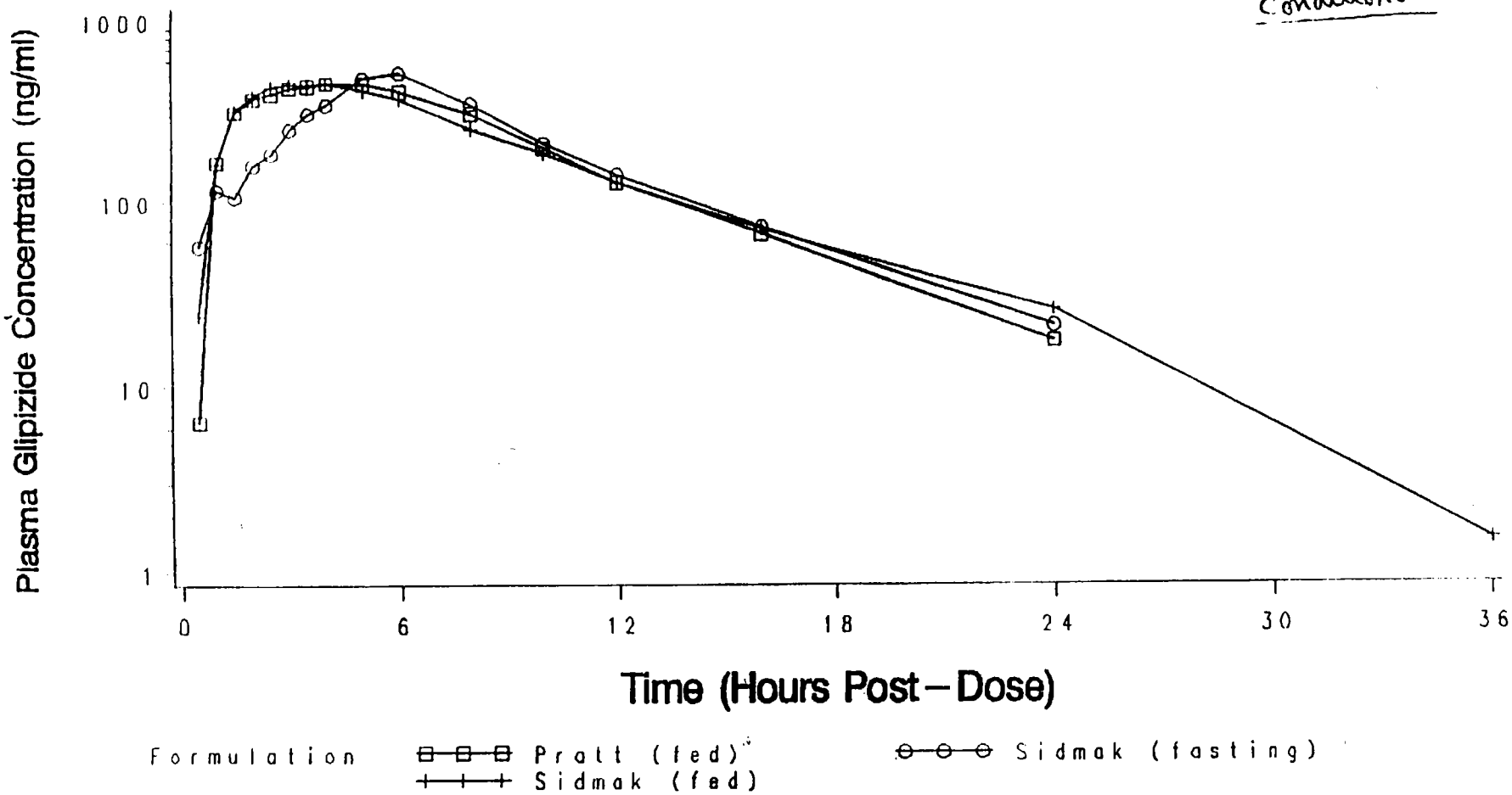
Figure 1

Project No. 930015

Mean Plasma Glipizide Concentrations

(Semi – Log Plot)

Under Non-fasting Conditions



ANDA#74-619

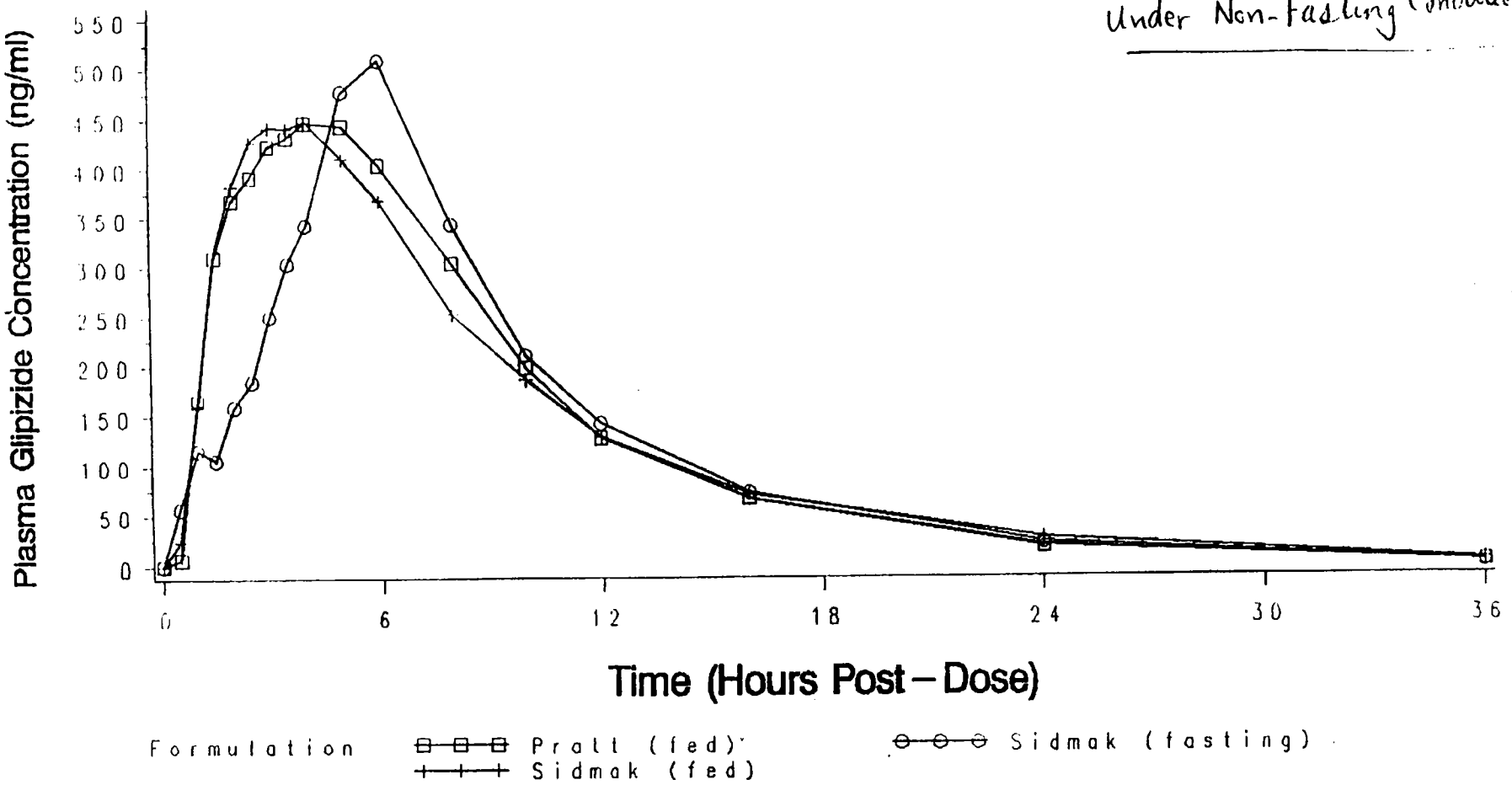
Figure 2

Project No. 930015

Mean Plasma Glipizide Concentrations

(Linear Plot)

Under Non-Fasting Conditions



NOV 22 1995 D IV

Glipizide
5 mg and 10 mg Tablets
ANDA #74-619
Reviewer: Z.Z. Wahba
wp#74619sdw.295

Sidmak Laboratories, Inc
E. Hanover, N.J.
Submission Date:
February 06, 1995
September 05, 1995

REVIEW OF AN IN VIVO BIOEQUIVALENCE STUDY, IN VITRO DISSOLUTION TESTING DATA AND A WAIVER REQUEST

I. OBJECTIVE:

To review:

1. Sidmak's *in vivo* bioequivalence studies under fasting conditions comparing its 10 mg strength Glipizide Tablets to the reference listed product, Pfizer's Glucotrol® Tablets 10 mg.

2. Dissolution data for 10 mg and 5 mg strength test and reference drug products.

3. Waiver request for the 5 mg strength tablets.

II. BACKGROUND:

Glipizide is a sulfonylurea antidiabetic agent. It is used to lower blood glucose concentration in diabetic and non-diabetic individuals. The precise mechanism(s) of sulfonylurea antidiabetic agents has not been clearly established, but the drugs, including glipizide, initially appear to lower blood glucose concentration principally by stimulating secretion of endogenous insulin from beta cells of the pancreas.

Glipizide appears in the plasma or serum within 15-30 minutes and has average peak plasma or serum concentrations of approximately 310-450 ng/mL. Glipizide plasma concentrations occur 1-3 hours (with a range 1-6 hours) after a single oral dose. Food delays the absorption of the drug but does not affect peak serum concentrations achieved or the extent of absorption. The half life of elimination ranges from 2-4 hours in normal subjects, whether given intravenously or orally. Plasma glipizide levels of 20-90 ng/mL have been reported to be therapeutically effective. The drug does not accumulate in plasma on repeated oral administration. The metabolism of glipizide is extensive and occurs mainly in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Less than 10% unchanged glipizide is found in the urine.

Glipizide is indicated as an adjunct to diet for the control of hyperglycemia. Glipizide is commercially available as tablets of 5 mg or 10 mg, Glucotrol®, manufactured by Pfizer Inc.

III. BIOEQUIVALENCE STUDY UNDER FASTING CONDITIONS

(clinical study project #900671)

A. **Sponsor:**
Sidmak Laboratories
17 West Street,
East Hanover, N.J. 07936

Study site
Clinical/Analytical Facilities

[redacted]

Date of Sample Collection:
October 29, 1993 and November 05, 1993

Date of First Sample Analysis:
November 25, 1993

Date of Last Sample Analysis:
January 17, 1994

Duration of Sample Storage:
80 days

B. **Study design:**
Randomized, single dose, two-way crossover study, under fasting conditions.

C. **Subjects:**
Twenty four (24) healthy male subjects (plus two alternates) were enrolled and 25 subjects completed the clinical study. The subjects were in the range of 21 to 44 years of age, and their body weights were within ± 15% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

Subject Selection Criteria:
Only medically healthy subjects as determined by normal

history, physical examination, laboratory profiles and EKG were enrolled in the study.

Subject Exclusion Criteria:
Subjects were excluded from the study based on the following criteria:

1. History of cardiovascular, pulmonary, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, hematological, hepatic, renal, psychiatric disease.
2. History of diabetes mellitus or complications (diabetic ketoacidosis).
3. Hypersensitivity to glipizide or other sulfonylurea-type drugs.
4. History of alcohol or drug abuse within the last year prior to the beginning of the study.
5. Any subject on an abnormal diet during the 4 weeks preceding the study.
6. A history of chronic alcohol or drug addiction.
7. Use of tobacco in any form.
8. Blood donation within the past 14 days (if the amount exceeded 500 mL), or 3 months (if the amount exceeded 750 mL) or 6 months (if amount exceeded 100 mL) or one year (if amount exceeded 2000 mL) of the study.
9. Receiving any investigational drug within 28 days prior to period I dosing.

Subject Restrictions:

1. No subject took any medications, including OTC products for at least 7 days prior to the beginning of the study until completion of the study.
2. No alcohol, xanthine and caffeine containing foods and beverages were allowed, beginning 24 hours prior to dosing until completion of the study.

D. Treatment:

Test Product: 1 X 10 mg Sidmak's Glipizide Tablet, Lot #93-023T, Batch size (not given), assay potency (not given), content uniformity (not given), manufactured date (not given).

Reference Product: 1 X 10 mg Pfizer's Glucotrol® Tablet, Lot #28P009A, assay potency (not given), content uniformity (not given), expiration date: 8/1997.

Washout period: 7 days between doses.
A single 10 mg dose was given in each period of the study.

E. Drug, Food and Fluid Intake:

Subjects fasted overnight before dosing and for 4 hours thereafter. The subjects received their medication with 240 mL of ambient temperature sucrose solution (containing three teaspoons of sugar dissolved in 240 mL water). In order to offset hypoglycemic effects, a 60 mL of sugar solution was

administered at the following times after dosing: 0.25, 0.5, 0.75, 1, 1.25, 1.25, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75 and 4 hours. The sugar solutions were administered within 6 minutes prior to these scheduled times. In addition, sucrose solutions were given to subjects who exhibited symptoms of hypoglycemia or low glucose readings. Standard meals were provided at appropriate times thereafter (lunch at 4 hours post-dose, supper at 9 hours post-dose).

F. Subject Monitoring:

The subjects blood glucose levels were performed before dosing and at 1, 2, 4 and 6 hours post-dosing.

G. Assay Methodology:

[redacted]

[redacted]

[redacted]

H. **Blood sampling:**

Blood samples (10 mL each) were collected in Vacutainers containing EDTA at 0.0, 0.5, 1.0, 1.50, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10, 12, 16, 24 and 36 hours post-dosing. The plasma samples were separated, collected and promptly stored frozen at -22 °C until analysis.

I. **Glucose levels Monitoring:**

The subjects blood glucose levels were performed before dosing and at 1, 2, 4 and 6 hours post-dosing. The firm mentioned that no safety problems were encountered. Subjects blood glucose levels data were not included in the submission (see deficiencies section).

G. **In Vivo Results:**

Twenty four (24) healthy male subjects (plus two alternates) were enrolled and 25 subjects completed the clinical study. Subject #14 was withdrawn from the study (after 26 hours of dosing of Period I) by the medical director due to medical events (for further details see the Medical Events Attachment). Samples from subject #25 (alternate) were analyzed in place of

those from subject #14. Samples of Subject #26 were not analyzed. The data set used for statistical analysis contained data from 24 subjects (subjects #1-13 and 15-25). It is noted that one subject (subject #12, test product, Period I) had a non-zero value of 80.5 ng/mL for the glipizide level at baseline (Zero Hour) for test product.

K. **Adverse Events:**

The adverse reactions have been reported (ANDA #74619, vol. 1.1, section "Clinical Report") by the subjects with a possibility of linkage to the test or reference drug product. The adverse reactions were considered mild. Only one subject (#14, test treatment, period I) experienced a series of mild to moderate adverse events which commenced from 1.1 to 22.1 hours after dosing. Subject #14 was the only subject discontinued from the study due to a moderate hypoglycemic reaction to the study and the medical director withdrew the subject from the study. All adverse events are summarized in the attachments (C3).

L. **Data Analysis:**

The pharmacokinetic parameters of glipizide were analyzed using an analysis of variance. The statistical differences due to treatments, period, dosing sequence and subjects nested within sequence were evaluated for plasma glipizide concentrations, as well as the following parameters, AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and $T_{1/2}$. The 90% confidence interval and the ratios of the test/reference means were also determined.
The pharmacokinetic parameters of the plasma glipizide concentrations, as well as the following parameters, AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and $T_{1/2}$ are summarized in Tables #5-7.

Table 5
Mean Plasma Concentrations of Glipizide in 24 Subjects Under Fasting Conditions
Unit: ng/mL

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	3.35	16.43	0.00	0.00	.
0.5	141.60	120.15	118.79	86.02	1.19
1	231.53	167.48	217.11	127.23	1.07
1.5	333.33	246.28	256.78	148.60	1.30
2	340.51	236.31	322.40	166.99	1.06
2.5	344.56	216.72	345.44	175.27	1.00
3	377.50	223.87	388.12	171.24	0.97
3.5	390.84	218.34	417.04	182.74	0.94
4	398.05	196.17	**478.36**	224.92	**0.83**
5	**413.65**	223.61	433.59	212.61	**0.95**
6	350.19	162.41	392.70	202.00	0.89
8	342.12	256.50	375.51	270.81	0.91
10	284.88	213.34	341.90	263.28	0.83
12	218.16	187.28	233.89	214.36	0.93
16	145.52	187.35	114.93	106.76	1.27
24	51.28	67.44	55.03	87.63	0.93
36	14.17	29.98	27.82	77.09	0.51

MEAN1=test MEAN2=Reference RMEAN12=T/R ratio
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 6
TEST MEAN/REFERENCE MEAN RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	**5543.00**	**3781.28**	**5822.25**	**3965.54**	**0.95**
AUCI	**6266.63**	**4426.15**	**5967.77**	**3790.25**	**1.05**
CMAX	**622.01**	**204.27**	**631.09**	**218.23**	**0.99**
THALF	4.85	1.79	5.51	4.23	0.88
TMAX	4.31	2.00	5.00	2.51	0.86
KE	0.16	0.06	0.17	0.07	0.97
*LAUCT	4666.48	0.57	4794.61	0.62	0.97
*LAUCI	5194.72	0.61	5028.27	0.59	1.03
*LCMAX	590.44	0.33	593.31	0.37	1.00

MEAN1=Test mean MEAN2=Ref. mean RMEAN12=T/R ratios
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

Table 7
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
AUCT	**5543.00**	**5822.25**	**85.84**	**104.57**
AUCI	**5751.35**	**6062.80**	**86.19**	**103.54**
CMAX	**622.01**	**631.09**	**91.09**	**106.03**
*LAUCT	4666.48	4794.61	90.20	105.02
*LAUCI	4810.65	5091.75	89.06	100.22
*LCMAX	590.44	593.31	92.32	107.27

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
* The values represent the geometric means (antilog of the means of the logs).

1. The mean plasma glipizide levels reached a maximum level of concentration around 4-5 hour (see Table #5 and the attached Figures #1 and #2).

2. The arithmetic test/reference mean ratios for AUC_{0-t}, AUC_{0-inf} and C_{max} were 0.95, 1.05 and 0.99, respectively. The geometric test/reference mean ratios for AUC_{0-t}, AUC_{0-inf} and C_{max} were 0.97, 1.03 and 1.00, respectively (Table #6). The 90% confidence intervals for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were within the acceptable range of 80-125% (see Table #7).

   There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

3. The average values of $T_{1/2}$, T_{max} and K_{el} for the test product were comparable to the corresponding reference values (Table #6).

IV. FORMULATION COMPARISON:

Sidmak's comparative formulations for its drug product, Glipizide 5 mg and 10 mg tablets are summarized in Table #8.

Table 8. Formulation Comparison

Ingredient (mg/tab)	5 mg Tablet	10 mg Tablet
Glipizide, USP	5.25	10.5
Lactose Anhydrous NF	[redacted]	
Sodium Starch glycolate, NF ([redacted]		
Corn Starch NF		
Pregelatinized Starch NF		
[redacted]		
Microcrystalline Cellulose NF		
[redacted]		
Purified Water*		
Magnesium Stearate NF		
Colloidal Silicon Dioxide NF		
[redacted]		
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Total Tablet Weight	190.0	380.0

*Does not appear in the finished product.

The 5 mg strength is proportionally similar in its active and inactive ingredients to the 10 mg strength the subject of approval.

V. In Vitro Dissolution Testing:

The firm has submitted comparative dissolution data for its drug product, Glipizide Tablets, 5 mg and 10 mg, and the reference product, Pfizer's Glucotrol® Tablets, 5 mg, 10 mg.

Method:	apparatus II (Paddle) at 50 rpm
Medium:	Phosphate Buffer, pH 7.5
Temperature:	37°C ± 0.5°C
No. Units Tested:	12 tablets
Specification:	NLT [redacted] Q) is dissolved in 45 minutes
Reference product:	Pfizer's Glucotrol® Tablets, 5 mg, 10 mg.

The dissolution testing data conducted by Sidmak on its drug product, Glipizide Tablets, 5 mg and 10 mg are presented in Table #9.

Table 9. In Vitro Dissolution Testing

Drug (Generic Name): Glipizide Tablets
Dose Strength: 5 mg, 10 mg
ANDA No.: 74619
Firm: Sidmak
Submission Date: February 06, 1995
File Name: 74619s.295

I. Conditions for Dissolution Testing:

USP XXII Apparatus Basket: Paddle: X RPM: 50
No. Units Tested: 12 Tablets
Medium: Phosphate Buffer, pH 7.5 Volume: 900 mL
Specifications: NLT [redacted](Q) is dissolved in 45 minutes
Reference Drug: Glucotrol® Tablets (manufactured by Pfizer's)
Assay Methodology: not given

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #93-025T Strength(mg) 5			Reference Product Lot #28P015A Strength(mg) 5		
	Mean %	Range	%CV	Mean %	Range	%CV
15	96	[redacted]	1.4	102	[redacted]	1.7
30	102	[redacted]	1.6	107	[redacted]	0.9
45	105	[redacted]	1.2	106	[redacted]	1.9
60	105	[redacted]	1.4	108	[redacted]	1.2

Sampling Times (Minutes)	Test Product Lot #93-023T Strength(mg) 10			Reference Product Lot #28P009A Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
15	96	[redacted]	1.5	103	[redacted]	2.8
30	101	[redacted]	1.4	106	[redacted]	2.0
45	103	[redacted]	1.0	106	[redacted]	1.6
60	104	[redacted]	1.0	106	[redacted]	1.6

VI. COMMENTS:

1. Under fasting conditions: The firm's *in vivo* bioequivalence study under fasting conditions demonstrated that the test product, Sidmak's Glipizide Tablets, 10 mg and the reference drug product, Pfizer's Glucotrol® Tablets, 10 mg are bioequivalent. The 90% confidence intervals for the log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were all within the acceptable range of 80-125%.

2. Adverse Reactions: All subjects reported with different adverse

reactions from both test and reference drug products were judged by the medical director as not serious cases (for further details see the Medical Events Attachment).

VII. DEFICIENCIES

1. Limited Food Effect Study:
   Since glipizide is indicated as an adjunct to diet for the control of hyperglycemia, a food study is required to examine the effect of food on the tested drug product.

   The firm should conduct a single-dose post-prandial bioequivalence study comparing equal doses of the test and reference products. The study should be conducted in a random, three-treatment (Treatments 1&2: the test and reference products should be dosed immediately after standard breakfast, Treatment 3: the test product should be dosed under fasting conditions), three-period, cross-over design using a sufficient number of healthy subjects. A wash-out period should be at least two week between periods 1, 2, and 3 dosing.

2. Information on the batch/lot size for the test product, the assay potency and content uniformity data for both the test and reference products, in addition to the date of manufacturing the test product should be included.

3. A detailed description of the dissolution methodology (including type of equipments that were used) should be provided. In addition, the dates which dissolution analysis were performed should be provided. It should be noticed that the Division of Bioequivalence considers the current USP methodology to be the regulatory method which must be used for dissolution comparison.

4. The following items are missing from the submission:
   a. The raw data of subjects blood glucose levels
   b. Table #T4.1
   c. Intraday assay validation data.

5. [redacted]

VI. RECOMMENDATIONS:

The in vivo bioequivalence study conducted by Sidmak Laboratories, Inc. under fasting conditions on its drug product, Glipizide Tablets, 10 mg comparing it to the reference drug product, Pfizer's Glucotrol® Tablets 10 mg has been found incomplete by the Division of Bioequivalence for the deficiencies cited above (#1-5).

The firm should be informed of the deficiencies and recommendations.

[redacted]

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE [redacted]
FT INITIALED RMHATRE [redacted] 11/22/95

Concur: [redacted] Date: _____
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #74-619 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Wahba), Drug File, Division File
ZZWahba/103095/112195/file #745619sdw.295

ANDA # 74-619
Glipizide

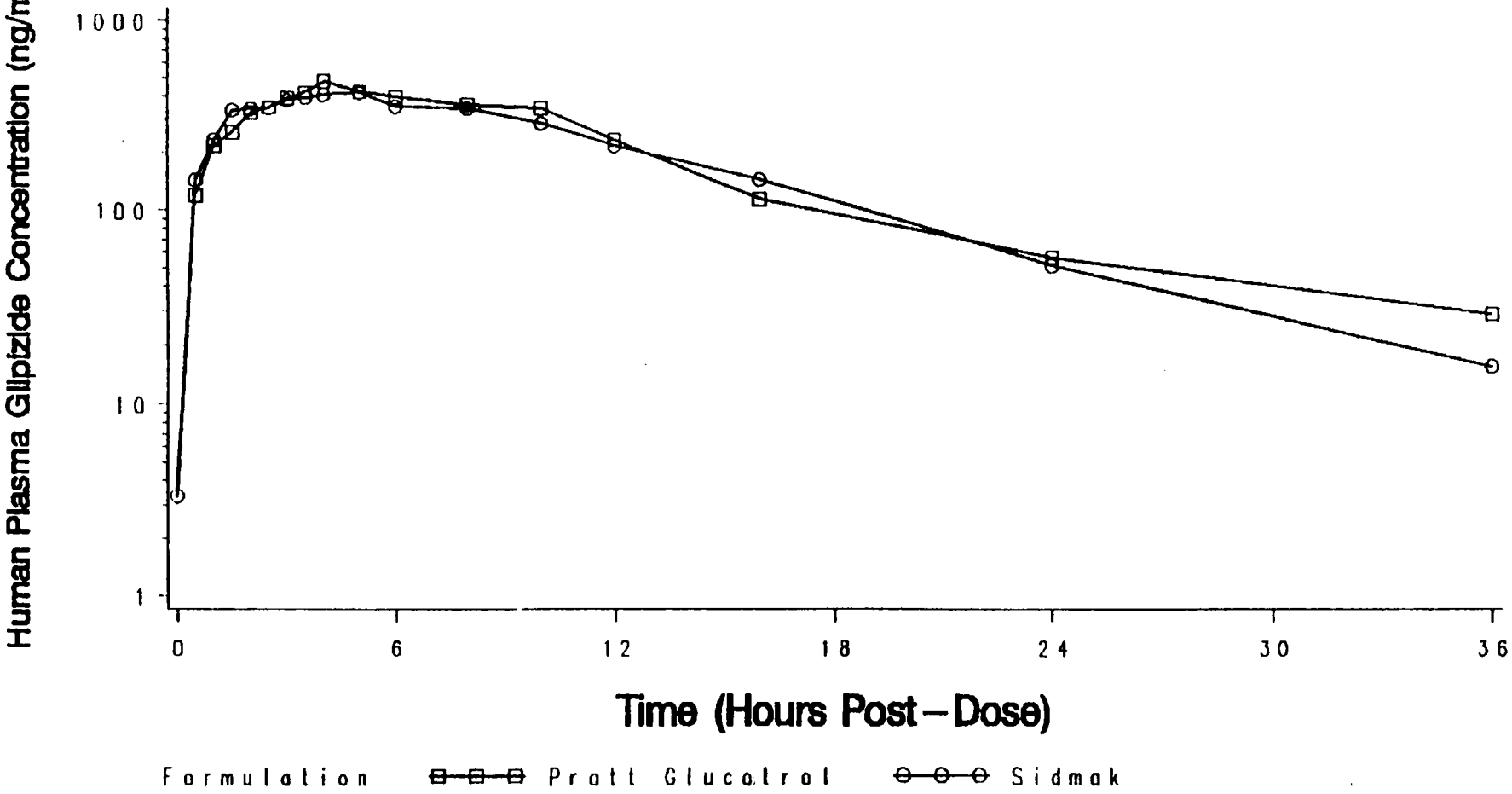
Figure 1

Project No. 900671

Mean Human Plasma Glipizide Concentrations

(Semi-Log Plot)

(N=24)



ANDA #74-619
Glipizide

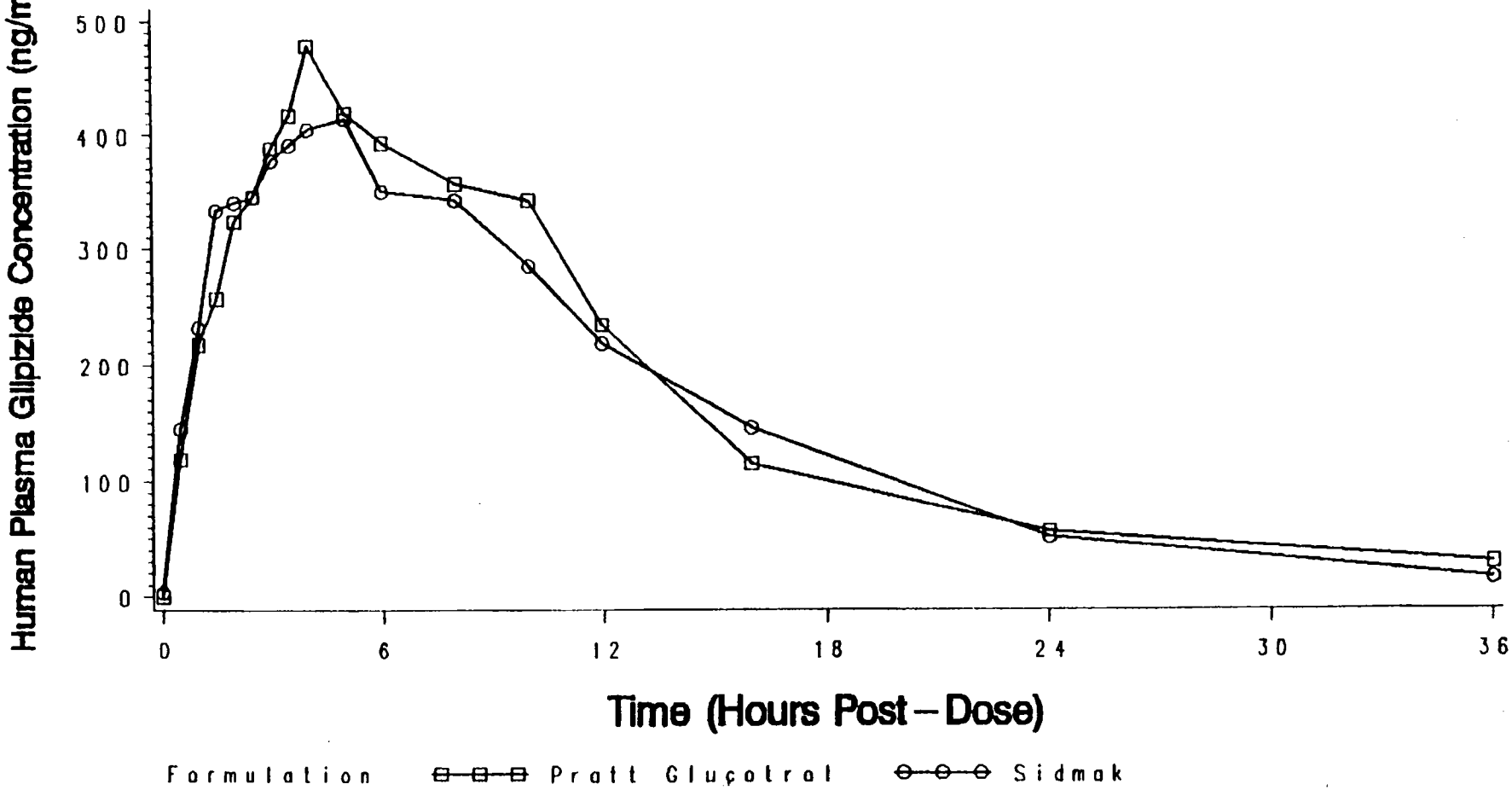
Figure 2

Project No. 900671

Mean Human Plasma Glipizide Concentrations

(Linear Plot)

(N=24)



ANDA # 74-619
Glipizide

ANDA# 74-619
Glipizide

TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing	Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Evolution	Intensity	Action / Comment
Product code A																
2	2	09:02:	05/11/93	**Headache**	2.5h	7.0h	NS	E	D	PR	SP	M	5.0h 9.5h	U R	M N/A	None
4	1	09:06:	29/10/93	**Headache**	24.0m	22.8h	NS	E	D	PR	SP	M	23.2h	R	N/A	
4	1	09:06:	29/10/93	**Felt nauseated** (4th cup of sucrose solution)	55.0m	3.0h	NS	E	P	D	SP	M	3.9h	R	N/A	Nausea stopped when finished drinking sucrose solution
					Associated with ingestion of hyperosmolar solution (sucrose)											
4	1	09:06:	29/10/93	**Shakiness**	1.9h	1.0h	NS	E	D	PR	SP	M	2.9h	R	N/A	
4	1	09:06:	29/10/93	**Fatigue**	6.9h	3.0h	NS	E	D	PR	SP	M	9.9h	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L.
A = Sidmak 1 x 10 mg glipizide tablet
B = Pratt (Glucotrol) 1 x 10 mg glipizide tablet

[redacted]

TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up Time after dosing	Evolution	Intensity	Action / Comment
Product code A															
4	1	09:06: 29/10/93	**Sorethroat** • Lost to follow up	2.1d	•	NS	U	O	PR	SP	M	7.0d	U	M	Temperature: 98.2 °F (36.8 °C)
								Probable intercurrent infection				7.5d	U	M	None
												8.0d	D	M	None
												8.5d	U	M	None
												26.0d			Lost to follow-up
5	2	09:08: 05/11/93	**Sensation of trembling in both legs**	7.4h	1.5h	NS	E	D	PR	SP	M	7.6h	U	M	Capillary glucose: 4.3; Subject very anxious; 1 x 60 mL sucrose solution
												8.9h	R	N/A	
5	2	09:08: 05/11/93	**Tremors of hands**	7.5h	1.3h	NS	E	D	PR	O	M	8.9h	R	N/A	
6	2	09:10: 05/11/93	**Feels sleepy**	7.8h	1.8h	NS	E	D	PR	SP	M	9.6h	R	N/A	
6	2	09:10: 05/11/93	**Hot flushes**	7.8h	1.8h	NS	E	D	PR	SP	M	9.6h	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
B = Pratt (Glucotrol) 1 x 10 mg glipizide tablet

TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Dur-ation	Serious-ness	Likeli-hood	Caus-ality	Proba-bility	Report method	Intensity at Onset	Follow-Up Time after dosing	Evol-ution	Int-ensity	Action / Comment
Product code A															
6	2	09:10: 05/11/93	**Shivering**	7.8h	1.8h	NS	E	D	PR	SP	M	9.6h	R	N/A	
6	2	09:10: 05/11/93	**Weakness**	7.8h	1.8h	NS	E	D	PR	SP	M	8.3h	U	M	Capillary glucose: 3.0 1 x 60 mL sucrose solution given
												9.6h	R	N/A	
7	1	09:12: 29/10/93	**Pain in left arm at venipuncture site** (antecubital area)	2.5h	2.3d	NS	E	P	D	SP	M	2.9h	U	M	Ice pack applied to area
												10.0h	U	M	None
												1.1d	D	M	None
												1.3d	D	M	None
												1.5d	U	M	None
												2.5d	R	N/A	
8	1	09:14: 29/10/93	**Palpitations**	5.9h	1.4h	NS	E	D	PR	SP	M	7.2h	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L

A = Sidmak 1 x 10 mg glipizide tablet

B = Pratt (Glucotrol) 1 x 10 mg glipizide tablet

[redacted]

TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing	Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Evolution	Intensity	Action / Comment
Product code A																
8	1	09:14:	29/10/93	**Headache** (forehead)	6.1h	5.9h	NS	E	D	PR	SP	M	7.2h	U	M	Capillary blood glucose: 4.5; 2 x 60 mL of sucrose solution given.
													7.3h	U	M	None
													10.0h	U	M	None
													12.0h	R	N/A	
8	1	09:14:	29/10/93	**Hot flushes**	6.1h	1.0h	NS	E	D	PR	SP	M	7.1h	R	N/A	
8	1	09:14:	29/10/93	**Tremors of hands**	6.4h	2.9h	NS	E	D	PR	SP	M	7.3h	D	M	None
													9.3h	R	N/A	
8	1	09:14:	29/10/93	**Headache**	15.0h	8.1h	NS	E	D	PR	SP	M	16.2h	U	M	Cold facecloth on forehead.
													23.1h	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
B = Pratt (Glucotrol) 1 x 10 mg glipizide tablet

TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Evolution	Intensity	Action / Comment
Product code A															
8	1	09:14: 29/10/93	**Headache**	1.5d	13.0h	NS	E	D	PO	E	M	2.1d	R	N/A	1 regular strength Tylenol was taken at 1.6 days post-dose
11	2	09:20: 05/11/93	**Tremors of hands**	2.3h	2.1h	NS	E	D	PR	SP	M	2.5h	U	M	None
												3.2h	U	M	None
												4.4h	R	N/A	
11	2	09:20: 05/11/93	**Headache**	4.4h	*	NS	E	D	PR	SP	M	6.0h	I	M	None
												*	R	N/A	However, resolved by 12.2 hr post-dose

* Time of resolution unknown

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
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TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up Time after dosing	Evolution	Intensity	Action / Comment
Product code A															
14	1	09:26: 29/10/93	**Feels dizzy**	1.1h	15.0m	NS	E	D	D	SP	M	1.2h	U	M	Was given 2 x 60 mL of sucrose solution at 1.1 hr post-dose
												1.2h	U	M	None
												1.3h	R	N/A	
14	1	09:26: 29/10/93	**Feels weak**	1.2h	11.0m	NS	E	D	D	SP	M	1.2h	D	M	None
												1.3h	R	N/A	
14	1	09:26: 29/10/93	**Headache**	2.0h	14.0m	NS	E	D	D	SP	M	2.2h	R	N/A	
14	1	09:26: 29/10/93	**Sensation of heat in his head**	2.0h	14.0m	NS	E	D	D	SP	M	2.2h	R	N/A	120 ml extra sucrose soluton given at 2.0 hr post-dose

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
B = Pratt (Glucotrol) 1 x 10 mg glipizide tablet

[redacted]

TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Dur-ation	Serious-ness	Likeli-hood	Caus-ality	Proba-bility	Report method	Intensity at Onset	Follow-Up Time after dosing	Evol-ution	Int-ensity	Action / Comment
Product code A															
14	1	09:26: 29/10/93	**Tremors of hands**	2.0h	14.0m	NS	E	D	D	SP	M	2.2h	R	N/A	60 mL sucrose solution given at 2.0 hr post-dose
14	1	09:26: 29/10/93	**Weakness**	2.0h	14.0m	NS	E	D	D	SP	M	2.2h	R	N/A	60 mL sucrose solution given at 2.0 hr post-dose
14	1	09:26: 29/10/93	**Slight sweating on forehead**	2.1h	6.0m	NS	E	D	D	O	M	2.2h	R	N/A	
14	1	09:26: 29/10/93	**Headache**	4.0h	4.8h	NS	E	D	D	N/R	M	6.1h	I	M	None
												7.1h	D	M	See Nurse's Notes
												8.8h	R	N/A	
14	1	09:26: 29/10/93	**Slight sweating on forehead**	4.0h	34.0m	NS	E	D	PO	SP	M	4.6h	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
B = Pratt (Glucotrol) 1 x 10 mg glipizide tablet

TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Evolution	Intensity	Action / Comment
Product code A															
14	1	09:26: 29/10/93	**Feels burning sensation in stomach**	4.6h	5.0h	NS	E	D	D	SP	M	7.2h	D	M	None
												9.6h	R	N/A	
14	1	09:26: 29/10/93	**Bloated feeling in stomach**	4.8h	*	NS	E	D	D	SP	M	7.2h	D	M	None
								* Resolve time and date unknown							
14	1	09:26: 29/10/93	**Sensation of heat all over body**	6.0h	2.8h	NS	E	D	D	SP	M	6.1h	D	M	Subject received 2 x 60 mL sucrose solution at 6.0 hr post-dose and 1 x 60 mL sucrose solution at 6.1 hr post-dose.
												7.2h	D	M	Subject given(50 mL) D50W IV push by DR. at 6.9 hr post-dose and started an IV (D5W) maintenance at 100 cc/hr by infusion pump.
												8.7h	R	N/A	See Nurse's Notes

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
B = Pratt (Glucotrol) 1 x 10 mg glipizide tablet

TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up Time after dosing	Follow-Up Evolution	Follow-Up Intensity	Action / Comment
Product code A															
14	1	09:26: 29/10/93	**Nausea**	6.0h	10.0m	NS	E	D	D	SP	M	6.2h	R	N/A	
14	1	09:26: 29/10/93	**Dizziness**	6.0h	54.0m	NS	E	D	D	SP	M	6.9h	R	N/A	See follow up "Sensation of heat all over body"
14	1	09:26: 29/10/93	**Blurred vision**	6.7h	18.0m	NS	E	D	D	SP	M	*	U	M	Capillary blood glucose: 2.3 at 6.7 hr post-dose; given 3 x 60 mL sucrose solution.
												7.0h	R	N/A	
14	1	09:26: 29/10/93	**Pale**	6.7h	34.0m	NS	E	D	D	O	M	7.2h	R	N/A	
14	1	09:26: 29/10/93	**Sweatiness**	7.6h	5.0m	NS	E	D	D	SP	MO	7.8h	I	MO	Received 50 cc D50% at 7.6 hr post-dose
												7.7h	R	N/A	

* Time and date of follow-up not recorded

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
B = Pratt (Glucotrol) 1 x 10 mg glipizide tablet

TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Dur-ation	Serious-ness	Likeli-hood	Caus-ality	Proba-bility	Report method	Intensity at Onset	Follow-Up Time after dosing	Evol-ution	Int-ensity	Action / Comment
Product code A															
14	1	09:26: 29/10/93	**Feels weak**	8.4h	20.0m	NS	E	D	D	SP	M	8.7h	R	N/A	Refer to Nurse's Notes
14	1	09:26: 29/10/93	**Sweatiness** (slightly sweaty)	8.4h	20.0m	NS	E	D	D	O	M	8.7h	R	N/A	Refer to Nurse's Notes
14	1	09:26: 29/10/93	**Diaphoretic**	9.3h	7.0m	NS	E	D	D	O	MO	9.5h	R	N/A	Refer to Nurse's Notes
14	1	09:26: 29/10/93	**Feeling weak**	9.3h	27.0m	NS	E	D	D	SP	MO	9.8h	R	N/A	Refer to Nurse's Notes
14	1	09:26: 29/10/93	**Looks pale**	9.3h	27.0m	NS	E	D	D	O	M	9.8h	R	N/A	Refer to Nurse's Notes
14	1	09:26: 29/10/93	**Sensation of heat all over body**	9.3h	7.0m	NS	E	D	D	SP	M	9.5h	R	N/A	Refer to Nurse's Notes

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
B = Pratt (Glucotrol) 1 x 10 mg glipizide tablet

[redacted]

TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Evolution	Intensity	Action / Comment
Product code A															
14	1	09:26: 29/10/93	**Slight soreness at the IV site** (left antecubital)	10.3h	*	NS	E	P	D	SP	M	26.1d	U	M	None
												32.3d	D	M	None
												*	R	N/A	*This is a long term recovery (over many months). For technical purposes, this medical event is deemed resolved at this date. (Medical director/ 39 d post-dose)
14	1	09:26: 29/10/93	**Dizziness**	13.1h	8.5h	NS	E	D	D	SP	M	21.6h	R	N/A	Refer to Nurse's Notes
14	1	09:26: 29/10/93	**Discomfort in left forearm** (when he flexes elbow)	22.1h	8.3h	NS	E	P	D	SP	M	1.0d	U	M	Hot compress applied to area of swelling
												1.3d	R	N/A	
14	1	09:26: 29/10/93	**Redness on left forearm**	22.1h	*	NS	E	P	D	O	M	*	R	N/A	

* Time of resolution unknown (no redness noted at 1 d post-dose)

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
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MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Dur-ation	Serious-ness	Likeli-hood	Caus-ality	Proba-bility	Report method	Intensity at Onset	Follow-Up Time after dosing	Evol-ution	Int-ensity	Action / Comment
Product code A															
14	1	09:26: 29/10/93	**Swelling of left forearm** (around IV site)	22.1h	1.1d	NS	E	P	D	SP	M	1.0d	U	M	Warm compresses applied to area
												1.1d	U	M	Warm compress to site, seen by doctor
												1.1d	U	M	Hot compress to site
												1.3d	D	M	None
												1.5d	D	M	None
												2.0d	R	N/A	
14	1	09:26: 29/10/93	**Discomfort in left forearm** (Hardness of vein in left hand (antecubital area)	2.0d	*	NS	E	P	D	SP	M	13.2d	I	M	Subject advised to see doctor and treat area with hot compress tid x 10-15 min.
									Residual thrombophlebitis, no other complication of hypertonic dextrose injection.			*	R	N/A	*This is a long term recovery (over many months). For technical purpose this medical event is deemed resolved at this date. (Medical Director/19 d post dose)

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
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MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up Time after dosing	Evolution	Intensity	Action / Comment
Product code A															
16	1	09:30: 29/10/93	**Dizziness**	1.5h	7.3h	NS	E	D	PR	SP	M	6.2h	I	M	2x 60 ml sucrose solution given; 6.0 hr blood glucose: 2.5 and follow up capillary glucose: 2.6 at 6.1 hr post-dose
												6.6h	D	M	Follow-up capillary blood glucose: 5.1 at 6.5 hr post-dose
												8.8h	R	N/A	
16	1	09:30: 29/10/93	**Tremors of hands**	1.5h	7.3h	NS	E	D	PR	SP	M	6.2h	U	M	See comments "Dizziness"
												6.6h	D	M	See same comments as above("Dizziness")
												7.4h	I	M	Capillary blood glucose: 3.1
												8.8h	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
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MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Evolution	Intensity	Action / Comment
Product code A															
16	1	09:30: 29/10/93	**Headache**	6.5h	17.0h	NS	E	D	PR	SP	M	10.1h	D	M	None
												23.5h	R	N/A	
19	1	09:36: 29/10/93	**Palpitations**	6.2h	5.8h	NS	E	D	PR	SP	M	6.3h	U	M	Pulse: 76
												6.4h	D	M	None
												7.5h	U	M	Radial pulse: 92 regular
												7.7h	U	M	None
												7.8h	U	M	Pulse: 76 regular
												10.1h	U	M	Pulse: 76 regular, BP: 130/70
												12.0h	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
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Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
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MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Evolution	Intensity	Action / Comment
Product code A															
19	1	09:36: 29/10/93	**Tremors of hands**	6.2h	5.8h	NS	E	D	PR	SP	M	6.3h	U	M	Given 2 x 60 mL of sugar solution
												6.3h	U	M	None
												6.4h	D	M	None
												7.7h	I	M	Given 2 x 60 mL of sucrose solution
												8.1h	D	M	Capillary blood glucose level: 4.6
												10.1h	U	M	None
												12.0h	R	N/A	
19	1	09:36: 29/10/93	**Weakness**	7.7h	2.9h	NS	E	D	PR	SP	M	10.1h	U	M	None
												10.2h	U	M	Capillary blood glucose: 3.1 at 10.1 hr post- dose
												10.5h	R	N/A	Capillary blood glucose: 3.8
20	2	09:38: 05/11/93	**Headache**	22.0m	7.8h	NS	E	D	PR	SP	M	6.0h	U	M	None
												8.1h	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
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Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
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TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up Time after dosing	Evolution	Intensity	Action / Comment
Product code A															
20	2	09:38: 05/11/93	**Weakness in right leg** (behind the knee)	22.0m	7.8h	NS	E	D	PR	SP	M	6.1h 8.1h	U R	M N/A	None

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
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TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up Time after dosing	Evolution	Intensity	Action / Comment
Product code B															
2	1	09:02: 29/10/93	**Dizziness**	2.5h	10.0m	NS	E	D	PR	SP	M	2.6h	D	M	Capillary blood glucose: 2.3. 60 ml of extra sucrose solution given; Semi - reclining with legs elevated.
												2.7h	U	M	Extra 120 ml of sucrose solution given
												2.6h	R	N/A	Subject stated the symptom was indeed resolved at the given time although the symptom was not resolved at previous follow-up.
2	1	09:02: 29/10/93	**Weakness in the thighs**	2.5h	20.0m	NS	E	D	PR	SP	M	2.8h	R	N/A	
2	1	09:02: 29/10/93	**Palpitations**	2.6h	3.0m	NS	E	D	PR	SP	M	2.6h	D	M	Radial pulse: 94 regular; Sucrose solution given.
												2.6h	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
B = Pratt (Glucotrol) 1 x 10 mg glipizide tablet

TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up Time after dosing	Evolution	Intensity	Action / Comment
Product code B															
2	1	09:02: 29/10/93	**Tremors of arms**	2.6h	20.0m	NS	E	D	PR	O	M	2.6h	U	M	See follow-ups, "Dizziness"
												*	D	M	See follow-ups, "Dizziness"
												2.9h	R	N/A	
4	2	09:06: 05/11/93	**Headache**												
			Subject described later as pressure in forehead												
				1.9h	21.5h	NS	E	D	PR	SP	M	5.0h	U	M	None
												6.1h	U	M	None
												12.2h	D	M	None
												23.4h	R	N/A	
4	2	09:06: 05/11/93	**Tremors of hands**	4.9h	30.0m	NS	E	D	PR	SP	M	5.4h	R	N/A	
5	1	09:08: 29/10/93	**Fatigue**	4.9h	4.0h	NS	E	D	D	SP	M	8.9h	R	N/A	
5	1	09:08: 29/10/93	**Feeling of bloated stomach**	6.2h	2.5h	NS	E	D	PR	SP	M	8.8h	R	N/A	

* exact time unknown (between 2.6 & 3.1 hrs post-dose)

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note. Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
B = Pratt (Glucotrol) 1 x 10 mg glipizide tablet

TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Evolution	Intensity	Action / Comment
Product code B															
5	1	09:08: 29/10/93	**Feels dizzy**	6.2h	2.4h	NS	E	D	PR	SP	M	6.4h	U	M	120 ml of sucrose solution given (200g/ 1 L of water); 3.1 mmol/L capillary blood glucose
												7.8h	D	M	None
												8.6h	R	N/A	
5	1	09:08: 29/10/93	**Feels heart beating fast**	6.2h	2.5h	NS	E	D	PR	SP	M	6.3h	U	M	IV 5% D/W start at 100 cc/hr, cath.# 22 infusing well
												6.4h	U	M	Pulse: 88 slightly irregular
												7.8h	I	M	Pulse: 102 irregular; BP: 110/50 Glucose: 2.6
												8.8h	R	N/A	Capillary blood glucose: 3.8
5	1	09:08: 29/10/93	**Headache**	13.9h	9.0h	NS	E	D	PR	SP	M	22.9h	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
B = Pratt (Glucotrol) 1 x 10 mg glipizide tablet

TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Dur-ation	Serious-ness	Likeli-hood	Caus-ality	Proba-bility	Report method	Intensity at Onset	Follow-Up Time after dosing	Evol-ution	Int-ensity	Action / Comment
Product code B															
6	1	09:10: 29/10/93	**Pulsating headache**	11.8h	3.3h	NS	E	D	PR	SP	M	13.4h 15.1h	D R	M N/A	None
11	1	09:20: 29/10/93	**Slight headache**	2.7h	1.9h	NS	E	D	PR	SP	M	4.6h	R	N/A	
16	2	09:30: 05/11/93	**Sensation of increased body heat**	47.0m	22.0m	NS	E	D	PR	SP	M	1.2h	R	N/A	
16	2	09:30: 05/11/93	**Dizziness**	52.0m	1.1h	NS	E	D	PR	SP	M	1.1h	U	M	1 x 60 mL sucrose solution given at 1.0 hr post-dose; Venous blood glucose: 2.0 Capillary blood glucose: 2.6
												1.2h 2.0h	D R	M N/A	1 x 60 mL sucrose solution given

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
B = Pratt (Glucotrol) 1 x 10 mg glipizide tablet

TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up Time after dosing	Evolution	Intensity	Action / Comment
Product code B															
16	2	09:30: 05/11/93	**Headache**	2.0h	21.3h	NS	E	D	PR	SP	M	3.1h	U	M	None
												4.1h	I	M	4 hr post-dose venous blood glucose: 3.1
												6.1h	D	M	None
												12.0h	I	M	None
												16.1h	U	M	Capillary blood glucose: 5.7
												23.3h	R	N/A	
19	2	09:36: 05/11/93	**Palpitations** (feels heart is beating very forcefully)	6.3h	3.1h	NS	E	D	PR	SP	M	6.4h	U	M	Radial pulse: 74 regular; Given 1 x 60 mL sucrose solution
												6.6h	D	M	None
												9.4h	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
B = Pratt (Glucotrol) 1 x 10 mg glipizide tablet

TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Evolution	Intensity	Action / Comment
Product code B															
19	2	09:36: 05/11/93	**Tremor of hands**	6.3h	3.1h	NS	E	D	PR	SP	M	6.5h	U	M	See follow-up "Palpitations" Capillary blood glucose: 3.0 at 6.4 hr post-dose
												6.6h	D	M	None
												9.4h	R	N/A	
19	2	09:36: 05/11/93	**Headache**	9.4h	13.0h	NS	E	D	PR	SP	M	22.4h	R	N/A	
20	1	09:38: 29/10/93	**Freezing, numb sensation in hands**	52.0m	1.0h	NS	E	D	PR	SP	M	1.3h	U	M	Given extra 60 mL sucrose solution Venous blood glucose: 2.6 at 1.0 hr post dose; follow-up capillary blood glucose 4.0 at 1.1 hr post-dose
												1.9h	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
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TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Evolution	Intensity	Action / Comment
Product code B															
20	1	09:38: 29/10/93	**Freezing, numb sensation in thighs**	52.0m	1.0h	NS	E	D	PR	SP	M	1.3h	U	M	See follow-up "Freezing, numb sensation in hands"
												1.9h	R	N/A	
20	1	09:38: 29/10/93	**Tightness in forehead**	1.1h	8.3h	NS	E	D	PR	SP	M	1.3h	U	M	See follow-up "Freezing, numb sensation in hands".
												3.0h	U	M	None
												9.4h	R	N/A	
20	1	09:38: 29/10/93	**Hardness, swelling on right arm** (venipuncture site)	1.0d	4.3h	NS	E	P	D	O	M	1.0d	U	M	Hot compresses applied to area
												1.1d	N/R	N/R	Hot compresses to area
												1.1d	U	M	Hot compresses to area
												1.2d	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
B = Pratt (Glucotrol) 1 x 10 mg glipizide tablet

TABLE C3 CLINICAL REPORT NO. 900671

MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Dur-ation	Serious-ness	Likeli-hood	Caus-ality	Proba-bility	Report method	Intensity at Onset	Follow-Up Time after dosing	Evol-ution	Int-ensity	Action / Comment
Product code B															
20	1	09:38: 29/10/93	**Hardness swelling on right arm** (under venipuncture site)	1.2d	4.0h	NS	E	P	D	SP	M	1.3d	D	M	Hot compress applied to area
												1.4d	R	N/A	
22	2	09:42: 05/11/93	**Sweaty palms**	30.0m	1.2d	NS	E	D	PR	SP	M	2.1h	U	M	Venous blood glucose: 2.9 at 2.0 hr post dose; Capillary blood glucose: 4.1 (2.1 hr post dose)
												3.0h	D	M	None
												6.1h	U	M	None
												12.0h	U	M	None
												1.0d	U	M	None
												1.2d	R	N/A	
22	2	09:42: 05/11/93	**Feet feel very cold**	1.8h	4.3h	NS	E	D	PR	SP	M	4.0h	U	M	None
												6.1h	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
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Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
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MEDICAL EVENTS

Subject	Period	Dosing Date/Time	Sign/Symptom	Time after dosing	Dur-ation	Serious-ness	Likeli-hood	Caus-ality	Proba-bility	Report method	Intensity at Onset	Follow-Up Time after dosing	Evol-ution	Int-ensity	Action / Comment
Product code B															
22	2	09:42: 05/11/93	**Sweaty forehead**	2.1h	*	NS	E	D	PR	O	M	2.1h	U	M	See follow-up "Sweaty palms"
				* Resolution time unknown								*	R	N/A	Symptom not present at 3.0 hr post-dose.
23	1	09:44: 29/10/93	**Sensation of heat over body**	6.1h	*	NS	E	D	PR	SP	M	6.2h	U	M	Venous blood glucose: 1.9 at 6.1 hr post dose; Follow-up capillary blood glucose: 2.7 at 6.1 hr post-dose; 1 x 60 mL sucrose solution given(6.2 hr post-dose) BP: 125/60, Pulse: 76
				* Resolve time unknown (between 6.2 hr & 10.0 hr post-dose)								*	R	N/A	
23	1	09:44: 29/10/93	**Sweating**	6.1h	6.0m	NS	E	D	PR	SP	M	6.2h	R	N/A	
24	1	09:46: 29/10/93	**Abdominal cramps** Intermittent	10.0m	4.6h	NS	E	D	PO	SP	M	4.7h	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

Note: Capillary and venous blood glucose values measured in mmol/L
A = Sidmak 1 x 10 mg glipizide tablet
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