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NDA 20482

PRECOSE

1 OF 3

NDA 20482

PRECOSE

NDA 20-482

SEP - 6 1995

Bayer Corporation
Pharmaceutical Division
Attention: Mr. William E. Maguire
Deputy Director, Regulatory Affairs
400 Morgan Lane
WEST HAVEN CT 06516-4175

Dear Mr. Maguire:

Please refer to your September 2, 1994, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Precose (acarbose tablets), 50 and 100 mg.

We acknowledge receipt of your amendments dated September 12, 27, 29, and 30, October 3, 5, 7, 10, 11, 12, 13, 14, and 17, and November 8 and 9, 1994; and January 17, March 13, 14, 22, and 31, April 10 (2), 20, 21, and 26, May 10, 12 and 22, June 9, 16, 19, and 27, July 5, 6, 17, and 19, August 10, and September 6, 1995 (2).

This new drug application as amended provides for the use of Precose as an adjunct to diet to lower blood glucose in patients with non-insulin-dependent diabetes mellitus (NIDDM) whose hyperglycemia cannot be managed by diet alone. It also may be used in combination with a sulfonylurea when diet plus either Precose or a sulfonylurea do not result in adequate glycemic control.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submissions dated September 2, 1994 (carton and container labels), and September 6, 1995 (package insert). Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on September 2, 1994 (carton and container labels), and September 6, 1995 (package insert). Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit fifteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-482. Approval of this labeling by FDA is not required before it is used.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Metabolism and Endocrine

Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and
Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

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

If you have any questions, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

J. Bilstad 9/6/95

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

MEMORY TRANSMISSION REPORT

TIME : SEP 06 '95 17:42
TEL NUMBER : 3014439282
NAME : FDA/CDER/DMEDP

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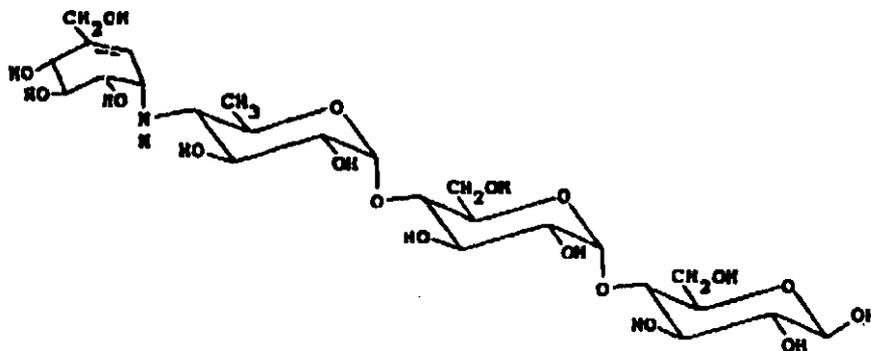
= change
from previous
9/6/95 Version

PROPOSED TEXT OF LABELING (PACKAGE INSERT)

PRECOSE™
(acarbose tablets)

DESCRIPTION

PRECOSE (acarbose tablets) is an oral alpha-glucosidase inhibitor for use in the management of non-insulin-dependent diabetes mellitus (NIDDM). Acarbose is an oligosaccharide which is obtained from fermentation processes of a microorganism, *Actinoplanes utahensis*, and is chemically known as O-4,β-dideoxy-4-[[[(1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1 → 4)-O-α-D-glucopyranosyl-(1 → 4)-D-glucose. It is a white to off-white powder with a molecular weight of 645.6. Acarbose is soluble in water and has a pK_a of 5.1. Its empirical formula is C₂₃H₄₃NO₁₆ and its chemical structure is as follows:



PRECOSE is available as 50 mg and 100 mg tablets for oral use. The inactive ingredients are starch, microcrystalline cellulose, magnesium stearate, and colloidal silicon dioxide.

CLINICAL PHARMACOLOGY

Acarbose is a complex oligosaccharide that delays the digestion of ingested carbohydrates, thereby resulting in a smaller rise in blood glucose concentration following meals. As a consequence of plasma glucose reduction, PRECOSE reduces levels of glycosylated hemoglobin in patients with Type II (non-insulin dependent) diabetes mellitus. Systemic nonenzymatic protein glycosylation, as reflected by levels of glycosylated hemoglobin, is a function of average blood glucose concentration over time.

Mechanism of Action: In contrast to sulfonylureas, PRECOSE does not enhance insulin secretion. The antihyperglycemic action of acarbose results from a competitive, reversible inhibition of pancreatic α -amylase and membrane-bound intestinal α -glucoside hydrolase enzymes. Pancreatic α -amylase hydrolyzes complex starches to oligosaccharides in the lumen of the small intestine, while the membrane-bound intestinal α -glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the brush border of the small intestine. In diabetic patients, this enzyme inhibition results in a delayed glucose absorption and a lowering of postprandial hyperglycemia.

Because its mechanism of action is different, the effect of PRECOSE to enhance glycemic control is additive to that of sulfonylureas when used in combination. In addition, PRECOSE diminishes the insulinotropic and weight-increasing effects of sulfonylureas.

Acarbose has no inhibitory activity against lactase and consequently would not be expected to induce lactose intolerance.

Pharmacokinetics:

Absorption: In a study of 6 healthy men, less than 2% of an oral dose of acarbose was absorbed as active drug, while approximately 35% of total radioactivity from a ^{14}C -labeled oral dose was absorbed. An average of 51% of an oral dose was excreted in the feces as unabsorbed drug-related radioactivity within 96 hours of ingestion. Because acarbose acts locally within the gastrointestinal tract, this low systemic bioavailability of parent compound is therapeutically desired. Following oral dosing of healthy volunteers with ^{14}C -labeled acarbose, peak plasma concentrations of radioactivity were attained 14-24 hours after dosing, while peak plasma concentrations of active drug were attained at approximately 1 hour. The delayed absorption of acarbose-related radioactivity reflects the absorption of metabolites that may be formed by either intestinal bacteria or intestinal enzymatic hydrolysis.

Metabolism: Acarbose is metabolized exclusively within the gastrointestinal tract, principally by intestinal bacteria, but also by digestive enzymes. A fraction of these metabolites (approximately 34% of the dose) was absorbed and subsequently excreted in the urine. At least 13 metabolites have been separated chromatographically from urine specimens. The major metabolites have been identified as 4-methylpyrogallol derivatives (i.e., sulfate, methyl, and glucuronide conjugates). One metabolite (formed by cleavage of a glucose molecule from acarbose) also has alpha-glucosidase inhibitory activity. This metabolite, together with the parent compound, recovered from the urine, accounts for less than 2% of the total administered dose.

Excretion: The fraction of acarbose that is absorbed as intact drug is almost completely excreted by the kidneys. When acarbose was given *intravenously*, 89% of the dose was recovered in the urine as active drug within 48 hours. In contrast, less than 2% of an *oral* dose was recovered in the urine as active (i.e., parent compound and active metabolite) drug. This is consistent with the low bioavailability of the parent drug. The plasma elimination half-life of acarbose activity is approximately 2 hours in healthy volunteers. Consequently, drug accumulation does not occur with three times a day (t.i.d.) oral dosing.

Special Populations: The mean steady-state area under the curve (AUC) and maximum concentrations of acarbose were approximately 1.5 times higher in elderly compared to young volunteers; however, these differences were not statistically significant. Patients with severe renal impairment ($Cl_{cr} < 25 \text{ mL/min/1.73m}^2$) attained about 5 times higher peak plasma concentrations of acarbose and 6 times larger AUCs than volunteers with normal renal function. No studies of acarbose pharmacokinetic parameters according to race have been performed. In U.S. controlled clinical studies of PRECOSE in patients with NIDDM, reductions in glycosylated hemoglobin levels were similar in whites (n=478) and blacks (n=167), with a trend toward a better response in hispanics (n=132).

Drug-Drug Interactions: Studies in healthy volunteers have shown that PRECOSE has no effect on either the pharmacokinetics or pharmacodynamics of digoxin, nifedipine, propranolol, or ranitidine. PRECOSE did not interfere with the absorption or disposition of the sulfonylurea glyburide in diabetic patients.

CLINICAL TRIALS

Clinical Experience in Non-Insulin-Dependent Diabetes Mellitus (NIDDM) Patients on Dietary Treatment Only: Results from six controlled, fixed-dose, monotherapy studies of PRECOSE in the treatment of NIDDM, involving 769 PRECOSE-treated patients, were combined and a weighted average of the difference from placebo in the mean change from baseline in glycosylated hemoglobin (HbA1c) was calculated for each dose level as presented below:

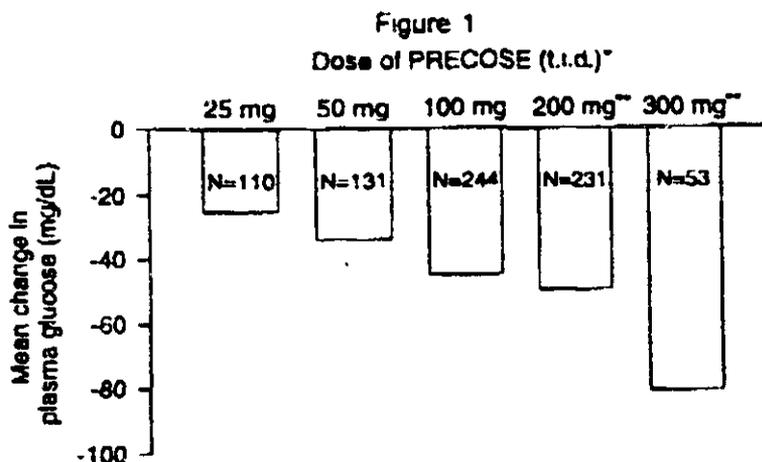
Table 1

Mean Change in HbA1c in Fixed-Dose Monotherapy Studies			
Dose of PRECOSE*	N	Change in HbA1c %	p-Value
25 mg t.i.d	110	-0.44	0.0307
50 mg t.i.d.	131	-0.77	0.0001
100 mg t.i.d.	244	-0.74	0.0001
200 mg t.i.d.**	231	-0.86	0.0001
300 mg t.i.d.**	53	-1.00	0.0001

* PRECOSE was statistically significantly different from placebo at all doses. Although there were no statistically significant differences among the mean results for doses ranging from 50 to 300 mg t.i.d., some patients may derive benefit by increasing the dosage from 50 to 100 mg t.i.d.

** Although studies utilized a maximum dose of 200 or 300 mg t.i.d., doses in excess of 100 mg t.i.d. are not recommended.

Results from these six fixed-dose, monotherapy studies were also combined to derive a weighted average of the difference from placebo in mean change from baseline for one-hour postprandial plasma glucose levels as shown in the following figure:



* PRECOSE was statistically significantly different from placebo at all doses with respect to effect on one-hour postprandial plasma glucose.

**The 300 mg t.i.d. PRECOSE regimen was superior to lower doses, but there were no statistically significant differences from 50 to 200 mg t.i.d.

Clinical Experience In NIDDM Patients Receiving Sulfonylureas: PRECOSE was studied as adjunctive therapy to sulfonylurea treatment in two large, placebo-controlled, double-blind, randomized studies conducted in the United States in which 540 patients were included in the efficacy analysis. In addition, PRECOSE was studied as adjunctive therapy to sulfonylurea treatment in a third study, conducted in Canada, in which patients were stratified according to background therapy. Study 1 (Table 2) involved patients under treatment at entry with diet alone who were subsequently randomized to four treatment groups. At the end of the study, patients in the PRECOSE + tolbutamide group showed a mean treatment effect on glycosylated hemoglobin (HbA1c) of -1.78% and were receiving a significantly lower mean daily dose of tolbutamide than patients in the tolbutamide-alone group. Also, the efficacy in the PRECOSE + tolbutamide group was significantly better than in the other three treatment groups. Study 2 (Table 2) involved patients taking background treatment with maximum daily doses of sulfonylureas. At the end of this study, the mean effect of the addition of PRECOSE to maximum sulfonylurea therapy was a change in HbA1c of -0.54 percent. In addition, there was a significantly greater proportion of patients in the PRECOSE + sulfonylurea group who reduced their sulfonylurea dose as compared to patients in the placebo + sulfonylurea group. In Study 3 (Table 2), the addition of PRECOSE to a background treatment of sulfonylurea produced an additional change in mean HbA1c of -0.8 percent.

Table 2

Study	Treatment	HbA _{1c} (%)*			p-Value
		Mean Baseline	Mean change from baseline	Treatment Difference**	
1	Placebo	9.48	+0.05	—	—
	PRECOSE 200† mg t.i.d.	9.19	-0.71	-0.76	0.0005
	Tolbutamide 250-1000 mg t.i.d. (mean dose 2.4 g/d)	9.28	-1.22	-1.27	0.0001
	PRECOSE 200† mg t.i.d. + Tolbutamide 250-1000 mg t.i.d. (mean dose 1.9 g/d)	8.99	-1.73	-1.78	0.0001
2	Sulfonylurea + Placebo	9.56	+0.24	—	—
	Sulfonylurea + PRECOSE 50-300† mg t.i.d.	9.64	-0.30	-0.54	0.0086
3	Sulfonylurea + Placebo	8.00	+0.10	—	—
	Sulfonylurea + PRECOSE 50-200† mg t.i.d.	8.10	-0.80	-0.90	0.0020

*Normal Range: 4-6%

** The result of subtracting the placebo group average

† Although studies utilized a maximum dose of 200 or 300 mg t.i.d., doses in excess of 100 mg t.i.d. are not recommended

INDICATIONS AND USAGE

PRECOSE, as monotherapy, is indicated as an adjunct to diet to lower blood glucose in patients with non-insulin-dependent diabetes mellitus (NIDDM) whose hyperglycemia cannot be managed on diet alone. PRECOSE may also be used in combination with a sulfonylurea when diet plus either PRECOSE or a sulfonylurea do not result in adequate glycemic control. The effect of PRECOSE to enhance glycemic control is additive to that of sulfonylureas when used in combination, presumably because its mechanism of action is different.

In initiating treatment for NIDDM, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling blood glucose and symptoms of hyperglycemia. The importance of regular physical activity when appropriate should also be stressed. If this treatment program fails to result in adequate glycemic control, the use of PRECOSE should be considered. The use of PRECOSE 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.

CONTRAINDICATIONS

PRECOSE is contraindicated in patients with known hypersensitivity to the drug and in patients with diabetic ketoacidosis. PRECOSE is also contraindicated in patients with inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or in patients predisposed to intestinal obstruction. In addition, PRECOSE is contraindicated in patients who have chronic intestinal diseases associated with marked disorders of digestion or absorption and in patients who have conditions that may deteriorate as a result of increased gas formation in the intestine.

PRECAUTIONS

General

Hypoglycemia: Because of its mechanism of action, PRECOSE when administered alone should not cause hypoglycemia in the fasted or postprandial state. Sulfonylurea agents may cause hypoglycemia. Because PRECOSE given in combination with a sulfonylurea will cause a further lowering of blood glucose, it may increase the hypoglycemic potential of the sulfonylurea. Oral glucose (dextrose), whose absorption is not inhibited by PRECOSE, should be used instead of sucrose (cane sugar) in the treatment of mild to moderate hypoglycemia. Sucrose, whose hydrolysis to glucose and fructose is inhibited by PRECOSE, is unsuitable for the rapid correction of hypoglycemia. Severe hypoglycemia may require the use of either intravenous glucose infusion or glucagon injection.

Loss of Control of Blood Glucose: When diabetic patients are exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of control of blood glucose may occur. At such times, temporary insulin therapy may be necessary.

Information for Patients: Patients should be told to take PRECOSE orally three times a day at the start (with the first bite) of each main meal. It is important that patients continue to adhere to dietary instructions, a regular exercise program, and regular testing of urine and/or blood glucose.

PRECOSE itself does not cause hypoglycemia even when administered to patients in the fasted state. Sulfonylurea drugs and insulin, however, can lower blood sugar levels enough to cause symptoms or sometimes life-threatening hypoglycemia. Because PRECOSE given in combination with a sulfonylurea or insulin will cause a further lowering of blood sugar, it may increase the hypoglycemic potential of these agents. The risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be well understood by patients and responsible family members. Because PRECOSE prevents the breakdown of table sugar, patients should have a readily available source of glucose (dextrose, D-glucose) to treat symptoms of low blood sugar when taking PRECOSE in combination with a sulfonylurea or insulin.

If side effects occur with PRECOSE, they usually develop during the first few weeks of therapy. They are most commonly mild-to-moderate gastrointestinal effects, such as flatulence, diarrhea, or abdominal discomfort and generally diminish in frequency and intensity with time.

Laboratory Tests: Therapeutic response to PRECOSE should be monitored by periodic blood glucose tests. Measurement of glycosylated hemoglobin levels is recommended for the monitoring of long-term glycemic control.

PRECOSE, particularly at doses in excess of 100 mg t.i.d., may give rise to elevations of serum transaminases. Such elevations have been transient or have been shown to be reversible upon discontinuation of the drug. If elevated transaminases are observed, a reduction in dosage or withdrawal of therapy may be indicated, particularly if the elevations persist.

Renal Impairment: Plasma concentrations of PRECOSE in renally impaired volunteers were proportionally increased relative to the degree of renal dysfunction. Long-term clinical trials in diabetic patients with significant renal dysfunction (serum creatinine >2.0 mg/dL) have not been conducted. Therefore, treatment of these patients with PRECOSE is not recommended.

Drug Interactions: Certain drugs tend to produce hyperglycemia and may lead to loss of blood glucose 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 PRECOSE, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from patients receiving PRECOSE in combination with sulfonylureas or insulin, patients should be observed closely for any evidence of hypoglycemia (see PRECAUTIONS).

Intestinal adsorbents (e.g., charcoal) and digestive enzyme preparations containing carbohydrate-splitting enzymes (e.g., amylase, pancreatin) may reduce the effect of PRECOSE and should not be taken concomitantly.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Nine chronic toxicity/carcinogenicity studies were conducted in three animal species (rat, hamster, dog) including two rat strains (Sprague-Dawley and Wistar).

In the first rat study, Sprague-Dawley rats received acarbose in feed at high doses (up to approximately 500 mg/kg body weight) for 104 weeks. Acarbose treatment resulted in a significant increase in the incidence of renal tumors (adenomas and adenocarcinomas) and benign Leydig cell tumors. This study was repeated with a similar outcome. Further studies were performed to separate direct carcinogenic effects of acarbose from indirect effects resulting from the carbohydrate malnutrition induced by the large doses of acarbose employed in the studies. In one study using Sprague-Dawley rats, acarbose was mixed with feed but carbohydrate deprivation was prevented by the addition of glucose to the diet. In a 26-month study of Sprague-Dawley rats, acarbose was administered by daily postprandial gavage so as to avoid the pharmacologic effects of the drug. In both of these studies, the increased incidence of renal tumors found in the original studies did not occur. Acarbose was also given in food and by postprandial gavage in two separate studies in Wistar rats. No increased incidence of renal tumors was found in either of these Wistar rat studies. In two feeding studies of hamsters, with and without glucose supplementation, there was also no evidence of carcinogenicity.

Acarbose showed no mutagenic activity when tested in six in vitro and three in vivo assays.

Fertility studies conducted in rats after oral administration produced no untoward effect on fertility or on the overall capability to reproduce.

Pregnancy:

Teratogenic Effects: Pregnancy Category B. The safety of PRECOSE in pregnant women has not been established. Reproduction studies have been performed in rats at doses up to 480 mg/kg (corresponding to 9 times the exposure in humans, based on drug blood levels) and have revealed no evidence of impaired fertility or harm to the fetus due to acarbose. In rabbits, reduced maternal body weight gain, probably the result of the pharmacodynamic activity of high doses of acarbose in the intestines, may have been responsible for a slight increase in the number of embryonic losses. However, rabbits given 160 mg/kg acarbose (corresponding to 10 times the dose in man, based on body surface area) showed no evidence of embryotoxicity and there was no evidence of teratogenicity at a dose 32 times the dose in man (based on body surface area). There are, however, no adequate and well-controlled studies of PRECOSE in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed. Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers: A small amount of radioactivity has been found in the milk of lactating rats after administration of radiolabeled acarbose. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, PRECOSE should not be administered to a nursing woman.

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

ADVERSE REACTIONS

Digestive Tract: Gastrointestinal symptoms are the most common reactions to PRECOSE. In U.S. placebo-controlled trials, the incidences of abdominal pain, diarrhea, and flatulence were 21%, 33%, and 77% respectively in 1075 patients treated with PRECOSE 50-300 mg t.i.d., whereas the corresponding incidences were 9%, 12%, and 32% in 818 placebo-treated patients. Abdominal pain and diarrhea tended to return to pretreatment levels over time, and the frequency and intensity of flatulence tended to abate with time. The increased gastrointestinal tract symptoms in patients treated with PRECOSE is a manifestation of the mechanism of action of PRECOSE and is related to the presence of undigested carbohydrate in the lower GI tract.

Elevated Serum Transaminase Levels: At doses of 50 mg t.i.d. and 100 mg t.i.d., the incidence of serum transaminase elevations with PRECOSE was the same as with placebo. In long-term studies (up to 12 months, and including PRECOSE doses up to 300 mg t.i.d.) conducted in the United States, treatment-emergent elevations of serum transaminases (AST and/or ALT) occurred in 15% of PRECOSE-treated patients as compared to 7% of placebo-treated patients. These serum transaminase elevations appear to be dose related. At doses greater than the highest recommended dose of 100 mg t.i.d., the incidence of serum transaminase elevations greater than three times the upper limit of normal was two to three times higher in the PRECOSE group than in the placebo group. These elevations were asymptomatic, reversible, more common in females, and, in general, were not associated with other evidence of liver dysfunction.

Although in clinical trials no difference was seen in the incidence of serum transaminase elevations between PRECOSE and placebo at doses less than or equal to 100 mg t.i.d., there have been rare spontaneous reports from post-marketing experience with 100 mg t.i.d. of marked transaminase elevations, which were reversible upon discontinuation of PRECOSE.

Other Abnormal Laboratory Findings: Small reductions in hematocrit occurred more often in PRECOSE-treated patients than in placebo-treated patients but were not associated with reductions in hemoglobin. Low serum calcium and low plasma vitamin B₆ levels were associated with PRECOSE therapy but were thought to be either spurious or of no clinical significance.

OVERDOSAGE

Unlike sulfonylureas or insulin, an overdose of PRECOSE will not result in hypoglycemia. An overdose may result in transient increases in flatulence, diarrhea, and abdominal discomfort which shortly subside. Because of the low bioavailability of PRECOSE and its mechanism of action, no serious systemic reactions are expected in the event of an overdose.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with PRECOSE or any other pharmacologic agent. Dosage of PRECOSE must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended dose of 100 mg t.i.d. PRECOSE should be taken three times daily at the start (with the first bite) of each main meal. PRECOSE should be started at a low dose, with gradual dose escalation as described below, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.

During treatment initiation and dose titration (see below), one-hour postprandial plasma glucose should be used to determine the therapeutic response to PRECOSE and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately three months. The therapeutic goal should be to decrease both postprandial plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of PRECOSE, either as monotherapy or in combination with sulfonylureas.

Initial Dosage: The recommended starting dosage of PRECOSE is 25 mg (half of a 50-mg tablet), given orally three times daily at the start (with the first bite) of each main meal.

Maintenance Dosage: Dosage of PRECOSE should be adjusted at 4-8 week intervals based on one-hour postprandial glucose levels and on tolerance. After the initial dosage of 25 mg t.i.d., the dosage can be increased to 50 mg t.i.d. Some patients may benefit from further increasing the dosage to 100 mg t.i.d. The maintenance dose ranges from 50 mg t.i.d. to 100 mg t.i.d. However, if no further reduction in postprandial glucose or glycosylated hemoglobin levels is observed with titration to 100 mg t.i.d., consideration should be given to lowering the dose. Once an effective and tolerated dosage is established, it should be maintained.

Maximum Dosage: In clinical trials, doses greater than 100 mg t.i.d. appeared to give slightly improved glycemic control but significantly increased the risk of elevated serum transaminase levels. Therefore, the 100 mg t.i.d. dose should not be exceeded.

Patients Receiving Sulfonylureas: Sulfonylurea agents may cause hypoglycemia. PRECOSE given in combination with a sulfonylurea will cause a further lowering of blood glucose and may increase the hypoglycemic potential of the sulfonylurea. If hypoglycemia occurs, appropriate adjustments in the dosage of these agents should be made.

HOW SUPPLIED

PRECOSE is available as 50mg or 100mg round tablets. Each tablet strength is white to yellow-tinged in color. The 50 mg tablet is scored on one side and coded with the word "PRECOSE" and "50" on the unscored side. The 100 mg tablet is unscored and is coded with the word "PRECOSE" and "100" on the same side. PRECOSE is available in bottles of 100 and in unit dose packages of 100.

	<u>Strength</u>	<u>NDC Code</u>	<u>Tablet Identification</u>
Bottles of 100	50 mg	0026-2861-51	PRECOSE 50
	100 mg	0026-2862-51	PRECOSE 100
Unit Dose	50 mg	0026-2861-48	PRECOSE 50
Packages of 100:	100 mg	0026-2862-48	PRECOSE 100

Do not store above 25°C (77°F). Protect from moisture. For bottles, keep container tightly closed.

Caution: Federal law prohibits dispensing without a prescription.

Bayer Corporation
 Pharmaceutical Division
 400 Morgan Lane
 West Haven, CT 06516 USA

SBA

SBA or

SBA EQUIVALENT

ARE NO LONGER NECESSARY

Section 14: This section is not applicable. All investigations relied upon by MILES in this NDA were conducted by or for MILES.

STATEMENT FOR SUBMISSION TO
US FDA FOR ACARBOSE

Section 13: Patents which claim the drug are as follows:

The drug, Acarbose, (Bay G 5421) is specifically covered by U.S. Patent No. 4,062,950 which expires December 13, 1994. The '950 patent covers the compound, the compound with an inert pharmaceutical carrier, the compound with an inert foodstuff-carrier and the method of using the compound to inhibit glucoside hydrolases in the digestive tract of humans and animals.

U.S. Patent No. 4,174,439 which expires November 13, 1996 is directed to a method for isolating Acarbose.

U.S. Patent No. 4,904,769 which expires February 27, 2007 covers the highly purified form of Acarbose.

EXCLUSIVITY SUMMARY FOR NDA # 20-482

SUPPL# N/A

Trade Name Precoce Tablets 50/100mg Generic Name acarbose

Applicant Name Bayer Corporation HFD# 510

Approval Date If Known 9/6/95

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES / X / NO / /

b) Is it an effectiveness supplement?

YES / / NO / X /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / X / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / X / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength and route of administration, previously been approved by FDA for the same use?

YES / / NO / X /

If yes, NDA # _____

Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

Is this drug product or indication a DESI upgrade?

YES / / NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration?

Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / X /

1. "yes" identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA _____

NDA _____

NDA _____

2. Combination product N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / _ / NO / _ /

"yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA _____

NDA _____

NDA _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer to "yes", then skip to

question 3(a). If the answer to 3(a) is "yes" for any investigations referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCK ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b) (2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES / / NO / /

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

If yes, explain: _____

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product. i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES / /	NO / /
Investigation #2	YES / /	NO / /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the for FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
 !
 IND # _____ YES /___/ ! NO /___/ Explain: _____
 !
 !
 Investigation #2
 IND # _____ YES /___/ ! No /___/ Explain: _____
 !
 !

(b) For each investigation not carried out under an IND or which the applicant was not identified as the sponsor, did applicant certify that it or the applicant's predecessor interest provided substantial support for the study?

Investigation #1 !
 !
 YES / / Explain: _____ ! NO / / Explain: _____
 !
 !
 _____ !
 _____ !
 Investigation #2 !
 !
 YES / / Explain: _____ ! NO / / Explain: _____
 !
 !
 _____ !
 _____ !

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

John R. Short

Signature John R. Short
Title: Consumer Safety Officer

7/14/95
Date

S. Sobel

Signature of Office/ S. Sobel, M.D.
Division Director Director, DMEDP

8/7/95
Date

cc: Original NDA

Division File

HFD-84

DEBARMENT CERTIFICATION

Miles hereby certifies under Section 301(k) (1) of the act (21 USC 335 a (k) (1)) that it did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) (section 306(a) or (b)), in connection with this NDA.

August 10, 1995

Memorandum

To: NDA 20-482 Precose (acarbose) Tablets

From: Solomon Sobel M.D. Director, Division of Metabolism and Endocrine Drug Products

Subject : Approval of NDA

HOO 10 1995

Solomon Sobel 8/10/95

This is the second time that this NDA has been submitted. The initial submission was withdrawn in 1990 after an Advisory Committee had recommended non-approval. At that time there were concerns raised about the safety of the drug in respect to its hepatic effects. In addition, questions were raised of the clinical significance of the modest effect on glycemic control and lack of dose response data.

These issues are adequately addressed in this re-submission of the NDA. It is clear that the elevation in serum enzymes seen with this drug can be avoided by keeping the dose at 100 mg. or below three times a day.

Dose response data show a flattening of effect at 100 mg tid and possibly even at 50 mg tid. The effect on glycosylated hemoglobin of about 0.8% with acarbose monotherapy may now be viewed in the context of the DCCT findings and can be accorded an anticipated effect in reducing diabetic complications.

Initially, there were some concerns raised about the oncogenicity of this drug. However subsequent to the original animal studies, it was well demonstrated that the renal adenocarcinomas and Leydig cell tumors seen in the studies with Sprague-Dawley rats were not caused by the chemical nature of the drug itself but rather were the result of glucose deprivation induced by the drug. Studies in Wistar rats did not show evidence of oncogenic effects. (this information appears in the labeling).

We believe that the indication can be granted for acarbose monotherapy as well as for combination with sulfonylureas. Although there are some data that would support metformin-acarbose combination therapy, the number of patients who were studied with this combination were small and we believe that this indication should be withheld until larger studies are done.

Recommendation:

Acarbose may be approved for patients with NIDDM.

The maximum dose should not exceed 100 mg three times a day.

Solomon Sobel



Group Leader's Note

While acarbose has modest efficacy, ^{causes} significant amounts of minor GI symptoms, and at high doses can cause liver injury; its overall risk/benefit relationship is probably more favorable than that of sulfonylurea agents. Because of its low potential for systemic effects, particularly cardiovascular, it is reasonable to attribute all the benefits associated with glycemic control in the DCCT to the extent that acarbose improves glycemic control. Thus, in the case of acarbose the benefits and risks are particularly well-defined and acceptable.

G Alexander Fleming MD
Group Leader
June 30, 1995

I have worked closely with Dr. Vignati and agree with all of his analyses and conclusions. He has added substantially to the understanding of this therapy's role and safe use.

A Fleming
6/30/95

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-482 Trade (generic) names Precose (Acarbose) Tablets 50/mg

Check any of the following that apply and explain, as necessary, on the next page:

1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.
2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(r) for A&MC studies in children.
- a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
- b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)
3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children):
- a. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols have been submitted and approved.
- (3) Protocols have been submitted and are under review.
- (4) If no protocol has been submitted, on the next page explain the status of discussions.
- b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

JUL 24 1995

Acarbose - NDA 20-482

Medical Officer's review of facsimile message from W E Maguire(Bayer) to Alexander Fleming(FDA) dated May 31, 1995

The attached material contains information about spontaneous reports of events involving the liver in patients taking acarbose. I reviewed this material when it was received and incorporated the pertinent information into my NDA review of June 30th 1995. Specific reference to this material is made in the package insert



Robert I Misbin MD
Medical Officer
July 19, 1995



attachment: facsimile dated May 31, 1995

Pharmaceutical
Division

Regulatory Affairs

Facsimile Message

Date: May 31, 1995

Subject: Acarbose -NDA 20, 498

From: W. E. Maguire

To: Alexander Fleming
FDA - Endocrine and Metabolic Division

Dear Dr. Fleming:

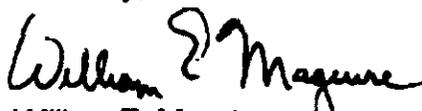
In response to your request of May 30, 1995, attached are 25 reports of spontaneous events for acarbose which involve the liver.

Twenty-two of these reports, describing 34 liver related events, are printouts from the Bayer international safety database. These events were included among the 207 reports in the Acarbose Safety Update that was submitted to FDA on May 10, 1995 and are included in our presentation to the advisory committee.

Three additional reports, 950158 (elevated LFT), 950714 (cholestatic jaundice), and 950158 (jaundice), which had not been included in the international safety database at the time the safety update was prepared but were subsequently received in West Haven, are also included in the attached information. Please note that these three reports are in a different format than the printouts from the safety database; however, the information included is the same for all reports.

If you have any questions regarding this information, please do not hesitate to call me at (703) 303-8719.

Sincerely,


William E. Maguire

SUSPECT ADVERSE REACTION REPORT

--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

I. REACTION INFORMATION

1. PATIENT INITIALS MR	COUNTRY Japan	2. DATE OF BIRTH Day Month Year	3a. AGE Years	3. SEX M	4.-6. REACTION ONSET Day Month Year	8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION <input type="checkbox"/> PATIENT DIED <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION <input type="checkbox"/> INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING
7. DESCRIBE REACTION(S) Dementia Eupatic function disorder		From 15.02.94 15.02.94	To 17.02.94 20.02.94	Duration days 44 days		
In about 20th of GlucoBay admin. patient showed no signs of dementia. At himself complained of anxiety. Lab		working. first GlucoBay. At the same time blood glucose control past 150 later events appear blood glucose control past.				
7b. CLINICAL Glucose stopped. GlucoBay 5mg/d started. Day 42 of GlucoBay. First GlucoBay received. Dementia disappeared.		Additional treatment. Parity discontinued.				
13. RELEVANT TESTS/LABORATORY DATA APPEARS THIS WAY ON ORIGINAL						

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) (Amoxicillin)		20. DID REACTION ABATE AFTER STOPPING DRUG? YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/>	
15. DAILY DOSE(S) 500 mg	16. ROUTE(S) OF ADMINISTRATION oral		21. DID REACTION REAPPEAR AFTER REINSTITUTION? YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/>
17. INDICATION(S) FOR USE Dementia treatment	18. THERAPY DATES (from-to/day, month, year) 18.12.93 - 22.02.94		
		19. THERAPY DURATION 67 days	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (include those used to treat reaction)	
Symptomatic	25 mg 24.04.91 continued
Clonidine	25 mg 24.04.91 continued
Insulin Glargine	60 mg 24.04.91 continued
Ethylenediamine succinate	3 T 24.04.91 continued
Metformin	0.1 mg 24.04.91 continued
23. OTHER RELEVANT HISTORY (e.g. diagnostic, allergic, pregnancy with last month of period, etc.) Concomitant diseases: Other relevant risk factors: Hypertension Angina pectoris Arteriosclerosis, cerebral Cerebral infarct	

REGULATORY SURVEILLANCE

APR 27 1995

IV. MANUFACTURER INFORMATION

24. NAME AND ADDRESS OF MANUFACTURER Bayer Japan 395-038	24b. BAYER CONTROL NO.: AMPHIBILE GLUCOBAY page 2/2 Incl. Comment	BAYER AG Pharma Research and Development Institute of Drug Safety 42006 Wuppertal, FRG
24c. DATE RECEIVED BY BAYER INC. 10.04.95	24d. REPORT SOURCE: <input type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> POST MARKETING SURVEILLANCE	
24e. DATE OF THIS REPORT 25.04.95	24e. REPORT TYPE: <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOW UP	

PATIENT NO.: 950022 SERIAL NO.: 1 (CONT.)

OTHER DETAILS OF EVENTS:
DESCRIBED SYMPTOMS: MEDICATION, CHOLESTASIS, INCREASED LIVER FUNCTION VALUES, SEVERE ITCHING (WHOLE BODY) WITHOUT ALERGIC EXANTHEMA. HOSPITALIZED 10.1.94-5.2.94.

CAUSE DUE TO OTHER CAUSES: _____

EVAMT TEST/LAB DATA:
11.1./1.2.94, 2.94, OPT 2.295/298/218
U/L GOT 77/80/75 U/L GLAMA OT 24/243/
248/270 U/L AP 147/816/782/892 U/L. LI-
BASE (2.93.2.94): 538/321 U/L.

INDICATION FOR USE: _____
CONCOMITANT DISEASE: _____
DIABETES
POLYNEUROPATHIA
HEPATITIS A. SEROLOG. NO DAMAGE (1961)
PLEXOPATHIA, LEFT ARM
ADIPOSIIS HEPATICA
NEPHROCYSTOSIS

TREATMENT: _____
FORMULATION: DAILY DOSE:

GLUCOBAY (ACARBOSE) 50 MG
GLUCON 100 MG
S 100 3 TAB
40 20 100 MG
AMAL 98 MG
IOCTACID 100 GH
1 APP

SK FACTOR: _____
EC. DIAGN. OR OTHER MEASURES: _____
ACTION FACTORS: _____
INITIAL REPORTER: _____
PORT TYPE: _____
WHICH AUTHORITY HAS INFORMED: _____

TOXICITY NO.: _____
C-NO.: _____
A-NO.: _____
YEAR ORIGIN NO.: _____
COUNTRY: _____
TREATMENT REFERENCE: _____
TELEPHONE: _____
ARMY/RE NO.: _____
PORT SOURCE: _____
DATE: FEB 2, 1995

OUTCOME COMMENTS:
PAT. RECOVERED AFTER WITHDRAWAL OF THOM-
BRAN AND GLUCOBAY. REPORTER, AE PROBABLY
RELATED TO GLUCOBAY, POSSIBLY TO THOMBRAN
AND EUOLUCON.

COMMENTS II COMMENTS:
AMS(S), ADEQUATE TEMPORAL
RELATIONSHIP. DD ADMIN. OF THOMBRAN, POS.
DECHALLENGE OF GLUCOBAY AND THOMBRAN.

APPLICATION: ORAL
ORAL
ORAL
ORAL
I.V.
DATE FROM: JAN 27, 1994
JAN 19, 1994
DATE TO: FEB 1, 1994
FEB 1, 1994
DURATION: 6 DAYS
14 DAYS
SINCE YEARS
LONGTERM
LONGTERM
LONGTERM

NOT NOTIFIED/INFORMED

INITIAL DATAPOOL INTERNATIONAL & PE 05.05.95
PATIENT NO.: 941831 SERIAL NO.: 1 PAT. INITIALS:

SEX: _____ MALE
WEIGHT (KG): _____
HEIGHT (CM): _____
DATE RECEIVED BY BAYER: _____ SEP 28, 1994
PROFESSION: _____
RACE: _____

ADVERSE REACTION: 1ST DOGT INCREASED
START DECODE: Gamma-GT increased
SITE FROM: _____
SITE TO: _____
INDICATION OF ADM: _____
TIME TO ONSET: _____
RELATIONSHIP TO DRUG: UNLIKELY
ADVERSE MEASURE: _____
OUTCOME: _____
DO REACT. REAPP. A. REINTROD.: _____
DIOUSNESS (AMS): _____
1ST SERIOUS EVENT (AMS): _____
REASON FOR SERIOUSNESS(AMS): _____
LABELLED (O-VERSION): _____

CONTINUED

PATIENT NO.: 941480 SERIAL NO.: J (CONT.)

ADDITIONAL DETAILS OF EVENTS:

CAUSE DUE TO OTHER CAUSES: _____

RELEVANT TEST/LAB. DATA: _____

INDICATION FOR USE: _____ DIABETES MELLITUS

CONCOMITANT DISEASE: _____

TREATMENT:

MCORAY (ACARBOSE)
IBENCLAMIDE
CARDIPINE

ACTION FACTORS: _____

INITIAL REPORTER: _____

REPORT TYPE: _____

WHICH AUTHORITY HAS INFORMED: _____

AUTHORITY NO.: _____

COUNTRY ORIGIN NO.: _____

COUNTRY: _____

LITERATURE REFERENCE: _____

TITLE: _____

BARCLINE NO.: _____

REPORT SOURCE: _____

DATE: _____

OUTCOME COMMENTS:
RECHALLENGE UNKNOWN.

CLONING II COMMENTS:
AMS: ADEQUATE
TEMPORAL SEQUENCE.

FORMULATION: DAILY DOSE:

3X50 MG
2X5 MG
2X20 MG

APPLICATION:

ORAL
ORAL
ORAL

DATE FROM:

APR 8, 1994

DATE TO:

MAY 18, 1994

DURATION:

INITIAL
OR: MCA
BAYER UK
309421

GREAT BRITAIN (GB)

MCA
JAN 3, 1995

CLINICAL DATAPOOL INTERNATIONAL & PE 03.05.95

PATIENT NO.: 941488 SERIAL NO.: 1 PAT. INITIALS: _____ DATE RECEIVED BY BAYER: _____ AUG 3. 1994
SEX: _____ PROFESSION: _____
AGE: _____ RACE: _____

MALE 73 YEAR(S) 77
ZND PAIN, ABDOMINAL
DIARRHEA
MAY 13, 1994
JUN 20, 1994

1ST POSSIBLE DRUG DISCONT. PERMANE.
DIARRHEA
MAY 13, 1994
JUN 20, 1994

2ND POSSIBLE DRUG DISCONT. PERMANE.
PAIN, ABDOMINAL
MAY 13, 1994
JUN 20, 1994

3RD POSSIBLE DRUG DISCONT. PERMANE.
LIVER FUNCTION TESTS ABNORMAL
LIVER FUNCTION test abnormal
MAY 13, 1994
JUN 20, 1994

4TH POSSIBLE DRUG DISCONT. PERMANE.
LIVER FUNCTION TESTS ABNORMAL
LIVER FUNCTION test abnormal
MAY 13, 1994
JUN 20, 1994

5TH POSSIBLE DRUG DISCONT. PERMANE.
LIVER FUNCTION TESTS ABNORMAL
LIVER FUNCTION test abnormal
MAY 13, 1994
JUN 20, 1994

6TH POSSIBLE DRUG DISCONT. PERMANE.
LIVER FUNCTION TESTS ABNORMAL
LIVER FUNCTION test abnormal
MAY 13, 1994
JUN 20, 1994

7TH POSSIBLE DRUG DISCONT. PERMANE.
LIVER FUNCTION TESTS ABNORMAL
LIVER FUNCTION test abnormal
MAY 13, 1994
JUN 20, 1994

8TH POSSIBLE DRUG DISCONT. PERMANE.
LIVER FUNCTION TESTS ABNORMAL
LIVER FUNCTION test abnormal
MAY 13, 1994
JUN 20, 1994

9TH POSSIBLE DRUG DISCONT. PERMANE.
LIVER FUNCTION TESTS ABNORMAL
LIVER FUNCTION test abnormal
MAY 13, 1994
JUN 20, 1994

10TH POSSIBLE DRUG DISCONT. PERMANE.
LIVER FUNCTION TESTS ABNORMAL
LIVER FUNCTION test abnormal
MAY 13, 1994
JUN 20, 1994

11TH POSSIBLE DRUG DISCONT. PERMANE.
LIVER FUNCTION TESTS ABNORMAL
LIVER FUNCTION test abnormal
MAY 13, 1994
JUN 20, 1994

12TH POSSIBLE DRUG DISCONT. PERMANE.
LIVER FUNCTION TESTS ABNORMAL
LIVER FUNCTION test abnormal
MAY 13, 1994
JUN 20, 1994

13TH POSSIBLE DRUG DISCONT. PERMANE.
LIVER FUNCTION TESTS ABNORMAL
LIVER FUNCTION test abnormal
MAY 13, 1994
JUN 20, 1994

14TH POSSIBLE DRUG DISCONT. PERMANE.
LIVER FUNCTION TESTS ABNORMAL
LIVER FUNCTION test abnormal
MAY 13, 1994
JUN 20, 1994

INTINUED

IDENT NO.: 940501 SERIAL NO.: 1 (CONT.)

OTHER DETAILS OF EVENTS:
DAY AFTER STARTING GLUCOBAY ONSET OF
REACTIONS: MCA, PROBABLY DUE TO KNOWN
GALLSTONES. SD RECOMMENCED.

WITH DUE TO OTHER CAUSES: _____
EVENT TEST/LAB DATA: _____

INDICATION FOR USE: _____
COMITANT DISEASE: _____
DIABETES MELLITUS
CHOLELITHIASIS
CHOLECYSTITIS
HYPERTENSION

TREATMENT: _____
FORMULATION: DAILY DOSE:
GLUCOBAY (ACARBOSE) 150 MG
GLAPRIL 10 MG
GLAZIDE 240 MG
GLIPIZINE 40 MG
FORMIN 40 MG
GLAR GUAREN 100

INDICATION FACTORS: _____
INITIAL REPORTER: _____
REPORT TYPE: _____
WHICH AUTHORITY WAS INFORMED: _____
7 (MCA)
INITIAL
CIOMS
GB: MCA
MILES USA
BAYER UK
BAYER I
BAYER A
MILES CDN
B701565

INDUSTRY: _____
COUNTRY: _____
REGISTRATION NO.: _____
REGISTRATION REFERENCE: _____
REGISTRATION NO.: _____
REPORT SOURCE: _____
GREAT BRITAIN (GB)
HEALTH PROFESSIONAL
MCA
APR 20, 1994

OUTCOME COMMENTS:
WITHDRAWAL OF GLUCOBAY, NEG RECHALLENGE.
AMS, FEVER (PYREXIA), VOMITING IN ADEQUATE
TEMPORAL SEQUENCE, CHALLENGE POS. JAUN-
DICE AND ABNORMAL HEPATIC FUNCTION AT-
TRIBUTABLE TO KNOWN GALLSTONES.

CIOMS II COMMENTS:
ATTRIBUTABLE TO GALLSTONE DISEASE

APPLICATION: _____
DATE FROM: _____ DATE TO: _____
ORAL JAN 5, 1994 JAN 7, 1994
ORAL SEP 7, 1993
ORAL JAN 12, 1993
ORAL AUG 27, 1991
ORAL SEP 28, 1993
DURATION:
3 DAYS
CONTINUOUS
CONTINUOUS
CONTINUOUS
CONTINUOUS

INITIAL DATAPool INTERNATIONAL & PE 05.05.95

PATIENT NO.: 940501 SERIAL NO.: 1 PAT. INITIALS:

SEX: _____ DATE RECEIVED BY BAYER: _____ APR 18, 1994
PROFESSION: _____
RACE: _____

AGE: _____
WEIGHT (KG): _____
HEIGHT (CM): _____
MALE
54 YEAR(S)
85

VERSE REACTION: 1ST
START DECODE: JAUNDICE
DATE FROM: Jaundice
DATE TO: JAN 6, 1994
RATIOSHIP OF ADR: JAN 9, 1994
DATE TO ONSET: 4 DAYS
RELATIONSHIP TO DRUG: UNLIKELY
ENTER MEASURE: DRUG DISCONT. PERMANE.
OUTCOME: REVERS.
D REACT. REAPP. A. REINTROD.: NO
D RIOUSNESS (AMS): NO
D ST SERIOUS EVENT (AMS): NO
D ASON FOR SERIOUSNESS(AMS): NO
D BELLED (O-VERSION): NO (UNEXPECTED)

VERSE REACTION: 3RD
START DECODE: VOMITTING
DATE FROM: Vomitting
DATE TO: JAN 6, 1994
RATIOSHIP OF ADR: JAN 9, 1994
DATE TO ONSET: 4 DAYS
RELATIONSHIP TO DRUG: POSSIBLE
ENTER MEASURE: DRUG DISCONT. PERMANE.
OUTCOME: REVERS.
D REACT. REAPP. A. REINTROD.: NO
D RIOUSNESS (AMS): NO
D ST SERIOUS EVENT (AMS): NO
D ASON FOR SERIOUSNESS(AMS): NO
D BELLED (O-VERSION): NO (UNEXPECTED)

2ND FEVER
Fever
JAN 6, 1994
JAN 9, 1994
4 DAYS
POSSIBLE
DRUG DISCONT. PERMANE.
REVERS.
NO

4TH LIVER FUNCTION TESTS ABNORMAL
Liver function test abnormal
JAN 6, 1994
JAN 9, 1994
4 DAYS
UNLIKELY
DRUG DISCONT. PERMANE.
REVERS.
NO
YES (EXPECTED)

CONTINUED

PATIENT NO.: 94009 SERIAL NO.: 1 (CONT.)

FURTHER DETAILS OF EVENTS:
PT DEVELOPED EVENTS DURING GLUCOBAY
THERAPY.

OUTCOME COMMENTS:
EVENTS CODED BY MCA. NO DETAILS FOR
REACTION. OUTCOME UNKNOWN. NO RECHALLENGE.
8.12.93 BAYER GB: FURTHER DETAILS
REQUESTED FROM MCA, AWAITING FOLLOW-UP
INFORMATION FROM DOCTOR.

DEATH DUE TO OTHER CAUSES: _____

RELEVANT TEST/LAB. DATA:

CIONS II COMMENTS,
POORLY DOCUMENTED, NAUSEA SECONDARY TO
NOT QUANTIFIED DISTURBANCE OF LIVER
FUNCTION?

INDICATION FOR USE, _____
CONCOMITANT DISEASE, _____
DIABETES MELLITUS

TREATMENT:

GLUCOBAY (ACARBOSE)
3LIBENCLAMIDE
4ETFORMIN
5NALAPRIL

FORMULATION: DAILY DOSE:
TABLET 150 MG
5 MG
100 MG
5 MG

APPLICATION: DRAL
DRAL
DRAL
DRAL
DATE FROM: SEP 10, 1993
DATE TO: SEP 25, 1993
DURATION: 16 DAYS

REACTION FACTORS: _____
INITIAL REPORTER: _____
REPORT TYPE: _____
WHICH AUTHORITY WAS INFORMED, _____

? INITIAL
CIONS
OB/MCA
MILES USA
BAYER UK
BAYER I
BAYER A
MILES COM
298952
940007
GREAT BRITAIN (GB)

AUTHORITY NO.: _____
BAYER ORIGIN NO.: _____
COUNTRY: _____
LITERATURE REFERENCE: _____
TITLE: _____
HARMLINE NO.: _____
REPORT SOURCE: _____

HEALTH PROFESSIONAL
BAYER GB
JAN 10, 1994

DATE: _____

PHARMACEUTICAL DATAPOOL INTERNATIONAL & PE 05.05.95
PATIENT NO.: 940009 SERIAL NO.: 1 PAT. INITIALS:

DATE RECEIVED BY BAYER: JAN 10, 1994
PROFESSION: _____
RACE: _____

SEX: _____
AGE: _____
HEIGHT (CM): _____
WEIGHT (KG): _____

MALE
74 YEAR(S)

ADVERSE REACTION:	1ST	HEPATIC FUNCTION ABNORMAL	2ND	NAUSEA
START DECODE:		Liver function test abnormal		reused
DATE FROM:		SEP 1993		SEP 1993
DATE TO:				
RELATIONSHIP TO DRUG:		INSUFF. EVIDENCE		PROBABLE
ADJUNCT MEASURE:		DRUG DISCONT. PERMANE.		DRUG DISCONT. PERMANE.
OUTCOME:				NO
REACT. REAPP. A. REINTROD.:				NO
SERIOUSNESS (AMS):				NO
1ST SERIOUS EVENT (AMS):				
REASON FOR SERIOUSNESS(AMS):				
LABELLED (0-VERSION):		YES (EXPECTED)		NO (UNEXPECTED)

CONTINUED

PATIENT NO.: 932298 SERIAL NO.: 1 (CONT.)

OTHER DETAILS OF EVENTS,
RECURRENT INCREASE GOT UP TO 27 AND OPT
UP TO 55.

CAUSE DUE TO OTHER CAUSES: _____

RELEVANT TEST/LAB DATA: _____

INDICATION FOR USE: _____

CONCOMITANT DISEASE: _____

TREATMENT: _____

UCOBAY (ACARBOSE)
INSULIN
PIRIN (CAPTOPRIL)
MONESIUM VERLA

SK FACTOR: _____
SK FACTOR: _____
SK FACTOR: _____
ACTION FACTORS: _____
INITIAL REPORTER: _____
REPORT TYPE: _____
COUNCIL AUTHORITY WAS INFORMED: _____
COUNCIL ORIGIN NO.: _____
COUNTRY: _____
TEMPERATURE REFERENCE: _____
TITLE: _____

ARMLINE NO.: _____
PORT SOURCE: _____
DATE: _____

DIABETES MELLITUS II

FORMULATION, DAILY DOSE:

3X100 MG
12.5 MG
3X1

SMOKER
ALCOHOL ABUSUS
ALLERGIC DISPOSITION
EGLSEER
INITIAL
BAYER A
M 13/93
AUSTRIA (A)

HEALTH PROFESSIONAL
BAYER A
FEB 9, 1994

OUTCOME COMMENTS:
AMS: POSSIBLE, CONSIDERED IN PACKAGE
INSERT.

CIGMS II COMMENTS:

APPLICATION: DATE FROM: DATE TO: DURATION:

ORAL (SUBCUTAN) MAY 1992 APR 27, 1993
S.C. MAY 1992 APR 27, 1993
ORAL MAY 1992 APR 27, 1993
ORAL MAY 1992 APR 27, 1993

NOT NOTIFIED/INFORMED

ORIGINAL DATAPOL INTERNATIONAL & PE 05.03.95
PATIENT NO.: 932298 SERIAL NO.: 1 PAT. INITIALS:

SEX: _____
AGE: _____
HEIGHT (CM): _____
WEIGHT (KG): _____
MALE YEAR(S)
44
159
67

DATE RECEIVED BY BAYER: _____
PROFESSION: _____
RACE: _____
DEC 17, 1993
ELECTRICIAN
CAUCASIAN (WHITE)

2ND
OPT INCREASED, RECURRENT
SOFT Ingressed
MAY 1992
APR 27, 1993

POSSIBLE
DRUG DISCONT. PERMANE.
REVERS.
NO
YES (EXPECTED)

1ST
OPT INCREASED, RECURRENT
SOFT Ingressed
MAY 1992
APR 27, 1993

POSSIBLE
DRUG DISCONT. PERMANE.
REVERS.
NO
YES (EXPECTED)

VERSE REACTION:
START DECODE:
SITE FROM:
SITE TO:
IRATION OF ADR:
TIME TO ONSET:
RELATIONSHIP TO DRUG:
LABOR MEASURE:
OUTCOME:
D REACT. REAPP. A. REINTROD.:
RIOUSNESS (AMS):
1ST SERIOUS EVENT (AMS):
ASON FOR SERIOUSNESS(AMS):
BELLED (D-VERSION):

CONTINUED

PHARMACEUTICAL DATAPOOL INTERNATIONAL & PE 05.05.95

PATIENT NO.: 931157 SERIAL NO.: 1 PAT. INITIALS:

SEX: _____

AGE: _____

WEIGHT (KG): _____

HEIGHT (CM): _____

MALE

78

175

82

DATE RECEIVED BY BAYER: _____

PROFESSION: _____

RACE: _____

JUL 12, 1993

PENSIONER

ADVERSE REACTION: 1ST BILIRUBIN INCREASE
START DECODE: Bilirubinemia
SITE FROM: MAY 2, 1993
SITE TO: 10 DAYS
ONSET: INSUFF. EVIDENCE
RELATIONSHIP TO DRUG: REVERS.
INTER MEASURE: NO
OUTCOME: NO (UNEXPECTED)
REACT. REAPP. A. REINTROD.:
DIOUSNESS (AMS):
1ST SERIOUS EVENT (AMS):
REASON FOR SERIOUSNESS(AMS):
RELLED (O-VERSION):

CONTINUED

TIENT NO. 930327 SERIAL NO. 1 (CONT.)

RYHER DETAILS OF EVENTS:
AFTER ABOUT 2 MONTHS ON GLUCOBAY TREAT-
MENT INCREASE OF LIVER ENZYMES SEEN.

OUTCOME COMMENTS:
WITHDRAWAL OF GLUCOBAY. DECLINING LAB
VALUES AFTERWARDS. DISCHARGE 28.10.92.

ATH DUE TO OTHER CAUSES: _____

LEVANT TEST/LAB DATA:
28.8/13/20.10.92: GAMMA-GT 56/402/280/
SOPT 13/86/55, AP -/377/223 U/L.

CIONS II COMMENTS:
POSITIVE DECHALLENGE; ALCOHOL ABUSE
SUSPECTED

ICATION FOR USE: _____
COMITANT DISEASE: _____
DIABETES MELLITUS II
PSYCHOSYNDROME, DEPRESSIVE, UNKNOWN ORIG.

EATMENT: _____

FORMULATION: DAILY DOSE:

UCOBAY (ACARBOSE)
GLUCON
ROXAT (PAROXETINE)
UCOPHAGE RETARD

500 MG
1/2-1 TAB
20 MG
1 TAB

APPLICATION:

ORAL
ORAL
ORAL
ORAL

DATE FROM:

AUG 6, 1992
SEP 4, 1992
SEP 28, 1992
OCT 5, 1992

DATE TO:

OCT 13, 1992

DURATION:

69 DAYS
CONTINUOUS
CONTINUOUS
CONTINUOUS

SK FACTOR: _____
ACTION FACTORS: _____
ITIAL REPORTER: _____
PORT TYPE: _____
ICH AUTHORITY WAS INFORMED: _____

ALCOHOL ABUSE ?

INITIAL
AMK D. AE
BGA
MILES USA
BAYER UK
BAYER A
113926
92015552

GERMANY (D)

K-NO.: _____
A-NO.: _____
YER ORIGIN NO.: _____
UNTRY: _____
TERATURE REFERENCE: _____
TLE: _____
ARMLINE NO.: _____
PORT SOURCE: _____
TE: _____

HEALTH PROFESSIONAL
BGA
MAY 18, 1996

INITIAL DATAPOOL INTERNATIONAL & PE 05.05.95

TIENT NO.: 930327 SERIAL NO.: 1 PAT. INITIALS:

X: _____ FEMALE

AGE (YR): _____ 66 YEAR(S)

WEIGHT (KG): _____ 156

HEIGHT (CM): _____ 171

DATE RECEIVED BY BAYER: _____ MAR 17, 1993
PROFESSION: _____
RACE: _____

VERSE REACTION: 157 LIVER ENZYMES INCREASE
 START DECODE: Liver function test abnormal
 DATE FROM: OCT 13, 1992

DATE TO: _____
 RATION OF ADR: _____
 TIME TO ONSET: _____
 RELATIONSHIP TO DRUG: _____
 INTER MEASURE: _____
 OUTCOME: _____
 DO REACT. REAPP. A. REINTROD.: _____
 SERIOUSNESS (AMS): _____
 IS IT SERIOUS EVENT (AMS): _____
 REASON FOR SERIOUSNESS(AMS): _____
 BELIEVED (O-VERSION): _____

INSUFF. EVIDENCE
 DRUG DISCONT. PERMANE.
 IMPROV.
 NOT APPLIC.
 YES

YES (EXPECTED)

CONTINUED

CLIENT NO.: 930526 SERIAL NO.: 1 (CONT.)

OTHER DETAILS OF EVENTS:
SINGLE SLIGHTLY INCREASED TRANSAMINASES
SEEN AFTER ABOUT 20 DAYS ON GLUCOBAY
THERAPY.

CAUSE DUE TO OTHER CAUSES: _____

LEVANT TEST/LAB DATA:
SGOT 9/24, SGPT 8/46, GAMMA-GT 25/66 U/L
(DAYS OF TESTS NOT INDICATED).

INDICATION FOR USE: _____
COMMITANT DISEASE: _____
DIABETES MELLITUS
CORONARY HEART DISEASE
HYPERTENSION, ARTERIAL
INFARCTION, POSTERIOR WALL (09/92)

TREATMENT: _____
FORMULATION, DAILY DOSE:

GLUCOBAY (ACARBOSE)
PIRIN (ASS)
PIRIN COR
NORMIN (ATEMOLOL)
RVATON RETARD
TABLET
50 MG
100 MG
12.5 MG
25 MG
8 MG

SK FACTOR: _____
DIET

ACTION FACTORS: _____
INITIAL REPORTER: _____
REPORT TYPE: _____
INITIAL
APK D. AE
BGA

CONTRACT NO.: _____
A. NO.: _____
113932
9201526

OTHER ORIGIN NO.: _____
COUNTRY: _____
GERMANY (B)

LITERATURE REFERENCE: _____

ANALYTICAL NO.: _____
HEALTH PROFESSIONAL
BOA
PORT SOURCE: _____
MAY 18, 1994

OUTCOME COMMENTS:
GLUCOBAY WITHDRAWN, OUTCOME NOT MENTIONED
PAT DISCHARGED 28.11.92.

CIDMS II COMMENTS:

APPLICATION: _____
ORAL
ORAL
ORAL
ORAL
ORAL
DATE FROM: NOV 6, 1992
NOV 25, 1992
NOV 18, 1992
DATE TO: NOV 27, 1992
DURATION: 22 DAYS
UNKNOWN
UNKNOWN

NOTIFIED/INFORMED

INITIAL DATAPOOL INTERNATIONAL & PE 05.05.95

PATIENT NO.: 930326 SERIAL NO.: 1 PAT. INITIALS:

SEX: _____ DATE RECEIVED BY BAYER: _____ MAR 17, 1993
AGE: _____ PROFESSION: _____
WEIGHT (KG): _____ RACE: _____

VERSE REACTION: 1ST TRANSMAMINASES INCREASED
START DECODE: Liver function test abnormal
DATE FROM: NOV 26, 1992
DATE TO: UNKNOWN
RELATIONSHIP TO DRUG: INSUFF. EVIDENCE
ONSET MEASURE: DRUG DISCONT. PERMANE.
REACT. REAPP. A. REINTROD.: NOT APPLIC.
SERIOUSNESS (AMS): NO
MOST SERIOUS EVENT (AMS):
REASON FOR SERIOUSNESS(AMS): YES (EXPECTED)
BELLEL (O-VERSION):

CONTINUED

PATIENT NO.: 938168 SERIAL NO.:) (CONT.)

ADDITIONAL DETAILS OF EVENTS:

CAUSE DUE TO OTHER CAUSES: _____

RELEVANT TEST/LAB. DATA:
BEFORE GLUCOBAY: GGT=40, OPT WITHIN NORMAL
RANGE, AFTER 1WK OF GLUCOBAY: GGT=98, OPT=_____
NO INFORMATION AT TIME OF REPORT

INDICATION FOR USE:
CONCOMITANT DISEASE: _____

TREATMENT: _____

GLUCOBAY (ACARBOSE)
TABLETS (TRIAMTEREN + HCL)

SK FACTOR: _____
ACTION FACTORS: _____
INITIAL REPORTER: _____

DIABETES MELLITUS (INSULIN DEP.)

KRUEGER DR.

INITIAL

REPORT TYPE: _____
WHICH AUTHORITY HAS INFORMED: _____

REPORTER ORIGIN NO.: _____
COUNTRY: _____

SIGNATURE REFERENCE: _____
TITLE: _____

ARMED NO.: _____
REPORT SOURCE: _____
DATE: _____

HEALTH PROFESSIONAL
MAR 1, 1993

OUTCOME COMMENTS:
REPORT: POSSIBLY OPT INCREASED.

ADDITIONAL COMMENTS:

APPLICATION: DATE FROM: DATE TO: DURATION:

TELEPHONE NO.: 08652/896

NOT NOTIFIED-INFORMED

FEB 16. 1993

DATE RECEIVED BY BAYER: _____
PROFESSION: _____
RACE: _____

MINICAL DATAPOL INTERNATIONAL & PE 05.05.95
PATIENT NO.: 938168 SERIAL NO.: 1 PAT. INITIALS:
FEMALE

AGE: _____
HEIGHT (CM): _____
WEIGHT (KG): _____

1ST GAMMA-GT INCREASED
Gamma-GT increased

ADVERSE REACTION:
START DECIDE:
DATE FROM:
DATE TO: OF ADR:
ONSET:
RELATIONSHIP TO DRUG:
LATER MEASURE:
OUTCOME:
D REACT REAPP. A. REINTROD.:
D RIOUSNESS (AMS):
ST SERIOUS EVENT (AMS):
ASON FOR SERIOUSNESS(AMS):
TELLED (O-VERSION):

INSUFF. EVIDENCE
NOT APPLIC.
NO

YES (EXPECTED)

CONTINUED

PATIENT NO.: 930094 SERIAL NO.: 1 (CONT.)

ADDITIONAL DETAILS OF EVENTS:
AFTER ABOUT 1 YEAR ON GLUCOBAY TREATMENT
INCREASED LIVER ENZYMES WERE NOTICED.

DEATH DUE TO OTHER CAUSES: _____

RELEVANT TEST/LAB. DATA:
07/92: OPT 41 U/L; GOT 41 U/L; GAMMA-GT
13 U/L.

INDICATION FOR USE: _____
CONCOMITANT DISEASE: _____
DIABETES MELLITUS II B
NONE

TREATMENT:

GLUCOBAY (ACARBOSE)
GLIBENCLAMIDE
GLUTHYROX

FORMULATION: DAILY DOSE:
100 MG TAB 300 MG
5.25 MG
0.1 MG

CAUTION FACTORS: _____
INITIAL REPORTER: _____
IGELBRINK, W. DR.

REPORT TYPE: _____
MICH. AUTHORITY HAS INFORMED: _____
AYER ORIGIN NO.: _____
COUNTRY: _____
LITERATURE REFERENCE: _____
TITLE: _____
HARMFUL TO: _____
REPORT SOURCE: _____
DATE: _____

OUTCOME COMMENTS:
WITHDRAWAL OF GLUCOBAY, VALUES NORMALIZED
AMS; ONLY LIMITED INTERPRETATION POSSIBLE.
NO INFORMAT. FOR DIFFERENTIAL DIAGNOSIS.

CIGMS II COMMENTS:

APPLICATION: ORAL
ORAL
ORAL
DATE FROM: JUL 1991
DATE TO: JUL 1992
DURATION: CA. 1 YEAR
CONTINUOUS
CONTINUOUS

TELEPHONE NO.: 02106/8971

HEALTH PROFESSIONAL
SALES REPRESENTATIVE
FEB 5, 1993

NOTIFIED/INFORMED

CLINICAL DATAPOOL INTERNATIONAL & PE 05.05.95

PATIENT NO.: 930094 SERIAL NO.: 1 PAT. INITIALS:

SEX: _____ MALE
AGE: _____ 61 YEAR(S)
HEIGHT (CM): _____ 173
WEIGHT (KG): _____ 72

DATE RECEIVED BY BAYER: _____ FEB 4, 1993
PROFESSION: _____ PENSIONER
RACE: _____

ADVERSE REACTION: 1ST SGOPT INCREASED
START DECODE: SGOPT increased
DATE FROM: JUL 1992
DATE TO:
DURATION OF ADR:
TIME TO ONSET:
RELATIONSHIP TO DRUG:
COUNTER MEASURE:
OUTCOME:
DID REACT, REAPP. A. REINTROD.:
SERIOUSNESS (AMS):
MOST SERIOUS EVENT (AMS):
REASON FOR SERIOUSNESS(AMS):
LABELLED (O-VERSION):

2ND SGOPT INCREASED
SGOPT increased
JUL 1992
POSSIBLE
DRUG DISCONT. PERMANE.
REVERS.
NOT APPLIC.
NO
YES (EXPECTED)

CONTINUED

PATIENT NO. 1 930093 SERIAL NO. 1 (CONT.)

URTHER DETAILS OF EVENTS:
AFT. ABOUT 7-8 MTHS ON GLUCOBAY TREATMENT
ONSET OF CEPHALGIA. ABOUT 1/2 YEAR
LATER INCREASE OF GPT AND GAMMA-GT WERE
NOTICED.

CAUSE DUE TO OTHER CAUSES: _____

RELEVANT TEST/LAB. DATA:
02/92: GPT 24 U/L; GAMMA-GT 24 U/L.
NEUROLOG. WITHOUT PATHOLOGICAL FINDINGS.

INDICATION FOR USE: _____
CONCOMITANT DISEASE: _____
DIABETES MELLITUS II
HYPERTENSION, ARTERIAL

FORMULATION: DAILY DOSE:

100 MG TAB 300 MG
5,25 MG 150 MG

TREATMENT:

GLUCOBAY (ACARBOSE)
GLUCUCON
ATAPRESAN

RISK FACTORS: _____
ACTION FACTORS: _____
INITIAL REPORTER: _____
HYPERLIPOPROTEINEMIA
IOELBRINK, W. DR.

REPORT TYPE: _____
HIGH AUTHORITY WAS INFORMED: _____
BY: _____
COUNTRY: _____
ITERATURE REFERENCE: _____
TITLE: _____
ANALYTICAL NO.: _____
REPORT SOURCE: _____

HEALTH PROFESSIONAL
SALES REPRESENTAT.
FEB 5, 1993

DATE: _____

OUTCOME COMMENTS:
WITHDRAWAL OF GLUCOBAY; ADVERSE EVENTS
RESOLVED. AMS, NO DETAILS GIVEN. NOT
ASSESSABLE. UNDELYING DISEASE ALSO CAN
CAUSE AE.

CIGMS II COMMENTS:
INADEQUATE TEMPORAL SEQUENCE; AFTER 7 -
8 MONTHS ON DRUG

DURATION:
CA. 15 MONTHS
CONTINUOUS
CONTINUOUS

APPLICATION: DATE FROM: DATE TO:
ORAL DEC 1990 FEB 1992
ORAL JAN 1991
ORAL MAR 1991

TELEPHONE NO.: 02106/8971

UNICAL DATAPDOL INTERNATIONAL & PE 05.05.95
PATIENT NO.: 950093 SERIAL NO.: 1 PAT. INITIALS: FEB 6, 1993
HOUSEWIFE

DATE RECEIVED BY BAYER: _____
PROFESSION: _____
RACE: _____

SEX: _____
AGE: 35 YEARS(S)
WEIGHT (KG): 160

2ND SOPT INCREASED
SOPT INCREASED
FEB 1992
FEB 1992

INSUFF. EVIDENCE
DRUG DISCONT. PERMANE.
REVERS.
NOT APPLIC.
NO

YES (EXPECTED)

CEPHALGIA
Headache
JUL 1991
FEB 1992
CA. 7 MONTHS

INSUFF. EVIDENCE
DRUG DISCONT. PERMANE.
REVERS.
NOT APPLIC.
NO

NO (UNEXPECTED)

GAMMA-OT INCREASE
Gamma-OT increased
FEB 1992
FEB 1992

INSUFF. EVIDENCE
DRUG DISCONT. PERMANE.
REVERS.
NOT APPLIC.
NO

YES (EXPECTED)

1ST
OVERSE REACTION:
START DECODE:
DATE FROM:
DATE TO:
DURATION OF ADR:
TIME TO ONSET TO DRUG:
RELATIONSHIP TO DRUG:
RELATIONSHIP TO DRUG:
DURIER MEASURE:
LYCONE:
ID REACT. REAPP. A. REINTROD.:

3RD
OVERSE REACTION:
START DECODE:
DATE FROM:
DATE TO:
DURATION OF ADR:
TIME TO ONSET TO DRUG:
RELATIONSHIP TO DRUG:
RELATIONSHIP TO DRUG:
DURIER MEASURE:
LYCONE:
ID REACT. REAPP. A. REINTROD.:

CONTINUED

PATIENT NO.: 921431 SERIAL NO.: 1 (CONT.)

FURTHER DETAILS OF EVENTS:
ENZYMES ELEVAT. BEFORE STARTING GLUCOBAY
DUE TO ALCOHOL/DRUG ABUSE 18.10.82
ADMISSION TO HOSPITAL DUE TO SUICIDE
ATTEMPT (ALCOHOL/ROHYPNOL).

OUTCOME COMMENTS:
TILL DATE OF REPORT (16.11.92) GLUCOBAY
WAS NOT YET STOPPED. NO INFORMATION ON
OUTCOME; PAT WAS DISCHARGED.

DEATH DUE TO OTHER CAUSES: _____

RELEVANT TEST/LAB. DATA:
AP > 400; GAMMA-GT > 100; TA < 100; BILLI
NORMAL; NO SYMPTOMS.

CIOMS II COMMENTS:
ALCOHOL ABUSE; SUICIDE ATTEMPT WITH
ALCOHOL/NEUROLEPTICS

INDICATION FOR USE: _____
CONCOMITANT DISEASE: _____
DIABETES MELLITUS

TREATMENT:

GLUCOBAY (ACARB(SE))
TRUXAL
ZYLORIC
EVOLUCON
DIPIPERON
MOOTROP
ROHYPNOL

FORMULATION: DAILY DOSE:
TABLET 2X 50 MG

APPLICATION: DATE FROM: DATE TO: DURATION:
ORAL OCT 22, 1992 CONTINUOUS

RISK FACTOR: _____
RISK FACTOR: _____
RISK FACTOR: _____
REACTION FACTORS: _____
INITIAL REPORTER: _____

ALCOHOL ABUSUS
DRUG ABUSE
ALCOHOL ABUSE (TILL 4 WEEKS AGO)
DRUG ABUSE: BENZODIAZEP. (TILL 4 WK AGO)
SUICID
CONCOMITANT DRUG SUSPECTED
MANNEMANN, H.-R. DR.

15-DAY-REPORT: _____
REPORT TYPE: _____
WHICH AUTHORITY HAS INFORMED: _____
BAYER ORIGIN NO.: _____
COUNTRY: _____
LITERATURE REFERENCE: _____
TITLE: _____
PHARM. NO.: _____
REPORT SOURCE: _____
DATE: _____

TELEPHONE NO.: 06051/600-541

NO
INITIAL
GERMANY (D)
HEALTH PROFESSIONAL:
NOV 19, 1992

CLINICAL DATAPool INTERNATIONAL & PE 05.03.95
 PATIENT NO. 721431 SERIAL NO.: 1 PAT. INITIALS:
 DATE RECEIVED BY BAYER: NOV 17, 1992
 PROFESSION: CAUCASIAN (WHITE)
 RACE:

SEX: _____
 AGE: _____
 HEIGHT (CM): _____
 WEIGHT (KG): _____
 MALE YEAR(S)
 78

2ND GAMMA-GT INCREASED
 Gamma-GT increased
 OCT 20, 1992
 NOV 11, 1992
 23 DAYS
 UNLIKELY
 NONE
 REVERS.
 NOT APPLIC.
 YES

LDH INCREASED
 Lactic dehydrogenase increased
 OCT 20, 1992
 NOV 11, 1992
 23 DAYS
 UNLIKELY
 NONE
 REVERS.
 NOT APPLIC.
 YES, BUT NOT MOST SERIOUS CONDITION

YES (EXPECTED)
 ALC. PHOSPHATASES INCREASED
 Alkaline phosphatase increased
 OCT 20, 1992
 NOV 11, 1992
 23 DAYS
 UNLIKELY
 NONE
 REVERS.
 NOT APPLIC.
 YES, BUT NOT MOST SERIOUS CONDITION

4TH
 YES (EXPECTED)
 GAMMA-GT INCREASE
 Gamma-GT increased
 OCT 20, 1992
 NOV 11, 1992
 23 DAYS
 UNLIKELY
 NONE
 REVERS.
 NOT APPLIC.
 YES, BUT NOT MOST SERIOUS CONDITION

YES (EXPECTED)
 YES (EXPECTED)

1ST
 ADVERSE REACTION:
 COSTARTY DECODE:
 DATE TO:
 DATE FROM:
 DURATION OF ADR:
 TIME TO ONSET:
 RELATIONSHIP TO DRUG:
 RELATIONSHIP TO DRUG:
 COUNTER MEASURE:
 OUTCOME:
 DID REACT. REAPP. A. REINTROD.:
 DID REACT. REAPP. A. REINTROD.:
 SERIOUSNESS (AMS):
 MOST SERIOUS EVENT (AMS):
 MOST SERIOUS EVENT (AMS):
 REASON FOR SERIOUSNESS(AMS):
 LABELLED (O-VERSION):

2ND
 ADVERSE REACTION:
 COSTARTY DECODE:
 DATE TO:
 DATE FROM:
 DURATION OF ADR:
 TIME TO ONSET:
 RELATIONSHIP TO DRUG:
 RELATIONSHIP TO DRUG:
 COUNTER MEASURE:
 OUTCOME:
 DID REACT. REAPP. A. REINTROD.:
 DID REACT. REAPP. A. REINTROD.:
 SERIOUSNESS (AMS):
 MOST SERIOUS EVENT (AMS):
 MOST SERIOUS EVENT (AMS):
 REASON FOR SERIOUSNESS(AMS):
 LABELLED (O-VERSION):

3RD
 ADVERSE REACTION:
 COSTARTY DECODE:
 DATE TO:
 DATE FROM:
 DURATION OF ADR:
 TIME TO ONSET:
 RELATIONSHIP TO DRUG:
 RELATIONSHIP TO DRUG:
 COUNTER MEASURE:
 OUTCOME:
 DID REACT. REAPP. A. REINTROD.:
 DID REACT. REAPP. A. REINTROD.:
 SERIOUSNESS (AMS):
 MOST SERIOUS EVENT (AMS):
 MOST SERIOUS EVENT (AMS):
 REASON FOR SERIOUSNESS(AMS):
 LABELLED (O-VERSION):

CONTINUED

PATIENT NO.: 921428 SERIAL NO.: 1 (CONT.)

FURTHER DETAILS OF EVENTS:
PT'S SON (PHYSICIAN) TOLD DR THAT
TRANSAMINASE LEVELS HAD BEEN ALWAYS
NORMAL.

OUTCOME COMMENTS:
GLUCOBAY CONTINUED, VENOSTASIN IV-FENIAT,
ERGOTOX STOPPED WHICH PT DID NOT NEED
ANYMORE. NORMAL TRANSAMINASES IN TEST
(29.10.92); 30.10.92: GLUCOBAY STOPPED DUE
TO SATISFIED BLOOD SUGAR VALUES.

DEATH DUE TO OTHER CAUSES:

RELEVANT TEST/LAB. DATA:
17.6.92: G. 14.9, 29.18, 92: OPT=156.39, AS/GOT=
101.18, 18: ALK.P. = 459.384, 150: GAMMA GT=
321.426, 41: TOTAL BILIRUBIN=0.78, 0.61,
0.59, 30.9.92: SMOORAPHY WITHOUT FINDINGS
NO LAB TEST BEFORE GLUCOBAY STARTED

INDICATION FOR USE: _____
CONCOMITANT DISEASE: _____
DIABETES MELLITUS : 1
HYPERTENSION, UNSTABLE
POLYNEUROPATHY, DIABETIC

TREATMENT:

GLUCOBAY (ACARBOSE)
EDGLUCON N
LANITOP E
DINHYDRO-SANOL-TRI
HEPA-MERZ
JOLAGORUM (??)

FORMULATION: ORAL-DOSE:
3X50 MG
1X1 TAB
1X1 TAB
TABLET
COATED TAB
GRANULATED POSX1 BAG
DROPS
2X20 DROPS

RISK FACTOR: _____
REACTION FACTORS: _____
INITIAL REPORTER: _____
INHERITED DISTURBANCE OF METABOLISM
CONCOMITANT DRUG SUSPECTED
BRAMMS, D. DR.

REPORT TYPE: _____
WHICH AUTHORITY WAS INFORMED: _____
BAYER ORIGIN NO.: _____
COUNTRY: _____
LITERATURE REFERENCE: _____
TITLE: _____
PHARMLINE NO.: _____
REPORT SOURCE: _____
DATE: _____
SALES REPRESENTAT.
NOV 25, 1992

CIOMS II COMMENTS:

DURATION:

APPLICATION: _____ DATE FROM: _____ DATE TO: _____
JRAL JUL 14, 1992 OCT 30, 1992
JRAL JUL 14, 1992 OCT 30, 1992
JRAL JUL 14, 1992 OCT 30, 1992
JRAL AUG 19, 1992 SEP 28, 1992
JRAL AUG 19, 1992 SEP 28, 1992

TELEPHONE NO.: 04941/2899

CLINICAL DATAPool INTERNATIONAL & PE 05.05.95
PATIENT NO.: 921428 SERIAL NO.: 1 PAT. INITIALS:

NOT NOTIFIED/INFORMED

SEX: _____
AGE: _____
HEIGHT (CM): _____
WEIGHT (KG): _____
FEMALE
87 YEAR(S)

DATE RECEIVED BY BAYER: _____
PROFESSION: _____
RACE: _____
NOV 17, 1992
PENSIONER
CAUCASIAN (WHITE)

ADVERSE REACTION: 1ST TRANSAMINASES INCREASED
COSTART DECODE: Liver function test abnormal
DATE FROM: JUL 14, 1992
DATE TO: OCT 30, 1992
DURATION OF ADR: UNLIKELY
TIME TO ONSET: NONE
RELATIONSHIP TO DRUG: IMPROV
COUNTER MEASURE: NOT APPLIC.
OUTCOME: NO
DID REACT REAPP. A. REINTROD.:
SERIOUSNESS (AMS):
MOST SERIOUS EVENT (AMS):
REASON FOR SERIOUSNESS(AMS):
LABELLED (O-VERSION): YES (EXPECTED)

CONTINUED

PATIENT NO. 920257 SERIAL NO. 1 (CONT.)

FURTHER DETAILS OF EVENTS:
POORLY DOCUMENTED.
CHANGES IN LAB VALUES DECLINED INSITE
OF CONTINUED TREATMENT WITH GLUCOBAY.
TEL. INFORM. (18.5.93) INCREASED TRANS-
MINASES (2-3X UNL) ALREADY BEFORE START
GLUCOBAY TREATMENT.

DEATH DUE TO OTHER CAUSES: _____

RELEVANT TEST/LAB DATA:
26.1.11.3.92; CHOL. 250-300; TRIGL 1700/
913; 224; GGT 80/42; CPK 120/85; AE.
LDH 238/170. NO CAB DATA BEFORE AE.

DIABETES MELLITUS

INDICATION FOR USE: _____

CONCOMITANT DISEASE: _____

TREATMENT: _____

GLUCOBAY (ACARBOSE)
LIPATHYL RETARD
INSULIN PROTAPHAN HM

RISK FACTOR: _____
REACTION FACTORS: _____
INITIAL REPORTER: _____

REPORT TYPE: _____
WHICH AUTHORITY HAS INFORMED: _____

BGA-NO. _____
BAYER ORIGIN NO. _____
COUNTRY: _____
LITERATURE REFERENCE: _____
TITLE: _____
PHARMLINE NO. _____
REPORT SOURCE: _____
DATE: _____

FORMULATION: DAILY DOSE:

50 MG TAB 3X 50 MG
250 MG CAPS 1X 250 MG
3x 250 IU

OUTCOME COMMENTS:
WITHDRAWAL OF GLUCOBAY. TRANSAMINASE
VALUES SLIGHTLY DECREASED TO PREVIOUS
VALUES (2-3X UNL). DOC'S TEL COMMENT:
GENERALLY NON COMPLIANT PAT WITH ALCOHOL
PROBLEMS.

CIOMS II COMMENTS:
MIGHT BE SECONDARY TO ALCOHOL ABUSE

APPLICATION: _____ DATE FROM: DEC 19, 1991 DATE TO: MAR 11, 1992
ORAL _____ DURATION: 97 DAYS
CONTINUOUS
CONTINUOUS

TELEPHONE NO.: 0211/786988

SMOKER _____
ALCOHOL ABUSE _____
KUEPPER, J. DR.

INITIAL _____
AMK B. AE
BOA
MILES USA
BAYER UK
BAYER I
9202576

GERMANY (D)

HEALTH PROFESSIONAL
SALES REPRESENTATIVE
APR 9, 1992

CLINICAL DATAPool INTERNATIONAL & PE 05.05.95
 PATIENT NO.: 920257 SERIAL NO.: 1 PAT. INITIALS:

SEX: _____ DATE RECEIVED BY BAYER: _____ APR 6, 1992
 AGE: 50 YEAR(S) PROFESSION: _____
 WEIGHT (KG): 148 RACE: _____
 HEIGHT (CM): 175

ADVERSE REACTION:	1ST	TRANSAMINASE INCREASE	NORSEMINO	2ND	HYPERLIPIDEMIA
CD START DECODE:		Aggravation reaction			Hyperlipemia
DATE FROM:		JAN 16, 1992			JAN 16, 1992
DATE TO:		MAR 11, 1992			MAR 11, 1992
DURATION OF ADR:		56 DAYS			56 DAYS
TIME TO ONSET:					
RELATIONSHIP TO DRUG:		UNLIKELY			UNLIKELY
COUNTER MEASURE:		DRUG DISCONT. PERMANE.			DRUG DISCONT. PERMANE.
OUTCOME:		NOT APPLIC.			IMPROV.
DID REACT. REAPP. A. REINTROD.:		NO			NO
SERIOUSNESS (AMS):					
MOST SERIOUS EVENT (AMS):					
REASON FOR SERIOUSNESS(AMS):		YES (EXPECTED)			NO (UNEXPECTED)
LABELLED (O-VERSION):					

CONTINUED

PATIENT NO.: 921205 SERIAL NO: 1 (CONT.)

FURTHER DETAILS OF EVENTS:
NO DRUG RELATED REACTIONS, BUT SEPSIS
WITH CHOLECYSTOLITHIASIS AND
CHOLANGIO-LITHIASIS,
INTERMITTENT ACUTE CHOLANGITIS

DEATH DUE TO OTHER CAUSES: _____
RELEVANT TEST/LAB DATA:

INDICATION FOR USE: _____
CONCOMITANT DISEASE: _____
DIABETES MELLITUS
CORONARY INSUFFICIENCY
VARIOSIS
LIVER PARENCHYMA DAMAGE

TREATMENT: _____
GLUCORAY (ACARBOSE)
NOVODIOL 0.2
DONA 200
FORMULATION: DAILY DOSE:
1X1
2X1

RISK FACTOR: _____
RISK FACTOR: _____
MULTIPLE ALLERGIC REACTIONS
DIABETES MELLITUS
HYPERLIPEMIA

REACTION FACTORS: _____
INITIAL REPORTER: _____
BUECHLER, E. DR.
INITIAL
GERMANY (D)

REPORT TYPE: _____
WHICH AUTHORITY HAS INFORMED: _____
BAYER ORIGIN NO.: _____
COUNTRY: _____
LITERATURE REFERENCE: _____
TITLE: _____
PHARMLINE NO.: _____
REPORT SOURCE: _____
DATE: _____
HEALTH PROFESSIONAL
OCT 28, 1992

OUTCOME COMMENTS: CHOLECYSTECTOMY WITH
RESOLVED AFTER CHOLEDOCHUS MEANWHILE
REVISION OF CHOLEDOCHUS MEANWHILE
THERAPY CHANGED TO INSULIN, NO MORE
PROBLEMS. DR. EVENT CAUSED BY
CHOLECYSTITIS/DIAGNOSE MENTIONED ABOVE.

CIONS II COMMENTS:
CHOLECYSTO - CHOLANGIOLITHIASIS;
SYMPTOMS RESOLVED AFTER CHOLECYSTECTOMY

APPLICATION: _____ DATE FROM: FEB 1991 DATE TO: JUN 1991 DURATION: ONGOING
ONGOING

TELEPHONE NO.: 06163/4990

CLINICAL DATAPOOL INTERNATIONAL & PE 05.05.95
 PATIENT NO.: 921295 SERIAL NO.: 1 PAT. INITIALS:

SEX: FEMALE
 AGE: 73 YEAR(S)
 HEIGHT (CM): 163
 WEIGHT (KG): 72

DATE RECEIVED BY BAYER: SEP 15, 1992
 PROFESSION: RETIRED, HOUSEWIFE
 RACE: CAUCASIAN (WHITE)

ADVERSE REACTION: CONSTANT DECODE: DATE FROM: DATE TO: DURATION OF ADR: RELATIONSHIP TO DRUG: COUNTER MEASURE: OUTCOME: DID REACT REAPP. A. REINTROD.: SERIOUSNESS (AMS): MOST SERIOUS EVENT (AMS): REASON FOR SERIOUSNESS(AMS): LABELLED (0-VERSION):	1ST Sepsis JUN 1, 1991 SEP 2, 1991 UNLIKELY DRUG DISCONT. PERM. + REM. THERAPY + OTHER REVERS. NOT APPLIC. YES NO (UNEXPECTED)	2ND EPIGASTRIC DISCOMFORT Abdominal pain JUN 1991 SEP 1991 UNLIKELY DRUG DISCONT. PERMAN. + OTHER P. H. + REV. NOT APPLIC. NO YES (EXPECTED)
ADVERSE REACTION: CONSTANT DECODE: DATE FROM: DATE TO: DURATION OF ADR: RELATIONSHIP TO DRUG: COUNTER MEASURE: OUTCOME: DID REACT REAPP. A. REINTROD.: SERIOUSNESS (AMS): MOST SERIOUS EVENT (AMS): REASON FOR SERIOUSNESS(AMS): LABELLED (0-VERSION):	3RD HYPOPALEMIA Hypoproteinemia JUN 1991 SEP 1991 UNLIKELY DRUG DISCONT. PERM. + REM. THERAPY + OTHER P. H. + REV. NOT APPLIC. YES, BUT NO MOST SERIOUS CONDITION NO (UNEXPECTED)	4TH CHOLESTIASIS Cholestatic jaundice JUN 1991 SEP 1991 UNLIKELY DRUG DISCONT. PERM. + REM. THERAPY + OTHER P. H. + REV. NOT APPLIC. YES, BUT NOT MOST SERIOUS CONDITION NO (UNEXPECTED)
ADVERSE REACTION: CONSTANT DECODE: DATE FROM: DATE TO: DURATION OF ADR: RELATIONSHIP TO DRUG: COUNTER MEASURE: OUTCOME: DID REACT REAPP. A. REINTROD.: SERIOUSNESS (AMS): MOST SERIOUS EVENT (AMS): REASON FOR SERIOUSNESS(AMS): LABELLED (0-VERSION):	5TH CONSCIOUSNESS, DISTURBED Confusion JUN 1991 SEP 1991 UNLIKELY DRUG DISCONT. PERM. + REM. THERAPY + OTHER P. H. + REV. NOT APPLIC. YES, BUT NO MOST SERIOUS CONDITION NO (UNEXPECTED)	

CONTINUED

PATIENT NO : 923966 SERIAL NO : 1 (CONT.)

FURTHER DETAILS OF EVENTS:

OUTCOME COMMENTS:
DR. INCREASED LIVER VALUES NOT RELATED TO
GLUCOBAY, BUT CAUSED BY SEVERE ALCOHOL
ABUSE.

DEATH DUE TO OTHER CAUSES: _____

RELEVANT TEST/LAB. DATA: _____

INDICATION FOR USE: _____

CONCOMITANT DISEASE: _____

TREATMENT: _____

GLUCOBAY (ACARBOSE)

RISK FACTOR: _____

REACTION FACTORS: _____

INITIAL REPORTER: _____

REPORT TYPE: _____

WHICH AUTHORITY HAS INFORMED: _____

BAYER ORIGIN NO. : _____

COUNTRY: _____

LITERATURE REFERENCE: _____

TITLE: _____

PHARMLINE NO. : _____

REPORT SOURCE: _____

DATE: _____

FORMULATION: DAILY DOSE: APPLICATION: DATE FROM: DATE TO: DURATION:

CIGARS II COMMENTS:

TELEPHONE NO. : 0311/763152

ALCOHOLABUSUS

MAEFEL. J. DR.

INITIAL

GERMANY (D)

HEALTH PROFESSIONAL
SALES REPRESENTAT.
OCT 27, 1992

NOT NOTIFIED/INFORMED

CLINICAL DATAPOOL INTERNATIONAL & PE 05.05.95
PATIENT NO.: 92(966 SERIAL NO.: 1 PAT. INITIALS:

SEX: _____
AGE: _____
HEIGHT (CM): _____
WEIGHT (KG): _____
DATE RECEIVED BY BAYER: _____ AUG 26, 1992
PROFESSION: _____
RACE: _____

ADVERSE REACTION: 1ST LIVER VALUES INCREASED
CONSTANT BECODE: Liver function test abnormal
DATE FROM: _____
DATE TO: _____
DURATION OF ADR: _____
TIME TO ONSET: _____
RELATIONSHIP TO DRUG: UNLIKELY
COUNTER MEASURE: _____
OUTCOME: NOT APPLIC.
DID REACT. REAPP. A. REINTROD.: NO
SERIOUSNESS (AMS): _____
MOST SERIOUS EVENT (AMS): _____
REASON FOR SERIOUSNESS(AMS): YES (EXPECTED)
LABELLED (0-VERSION): _____

CONTINUED

PATIENT NO.: 920747 SERIAL NO.: 1 (CONT.)

FURTHER DETAILS OF EVENTS,
NORMAL VALUES BEFORE STARTING GLUCOBAY,
INCREASE DURING THERAPY.

OUTCOME COMMENTS:
3 WEEKS AFTER WITHDRAWAL OF GLUCOBAY
RETURN TO NORMAL VALUES.
DOC COMMENT: NO OTHER CAUSE FOR ADR.

DEATH DUE TO OTHER CAUSES: _____

RELEVANT TEST/LAB DATA:
5/29 3/24.6.92: GOT 23/28/17; GPT 83/
102/62; GAMMA-GT (29.5.) 25.
SONOGRAPHY AND HEPATITIS SEROLOGY MAD.

INDICATION FOR USE: _____ DIABETES MELLITUS
CONCOMITANT DISEASE: _____

CIDMS II COMMENTS:

TREATMENT:

GLUCOBAY (ACARBDOSE) _____
FORMULATION, DAILY DOSE: _____
TABLET 3X100 MG

APPLICATION: _____ DATE FROM: _____ DATE TO: _____ DURATION: _____
ORAL OCT 30, 1991 JUN 3, 1992 218 DAYS

REACTION FACTORS:
INITIAL REPORTER: _____

REINART-LISSMANN, B. DR. _____ TELEPHONE NO.: _____/707949

15-DAY-REPORT: _____ NO
REPORT TYPE: _____ INITIAL
WHICH AUTHORITY WAS INFORMED: _____ BGA

SJA-NO.: _____ 92901258
BAYER ORIGIN NO.: _____ GERMANY (D)

COUNTRY: _____
LITERATURE REFERENCE: _____

TITLE: _____
PHARMLINE NO.: _____
REPORT SOURCE: _____
DATE: _____

HEALTH PROFESSIONAL
JUL 21, 1992

NOTIFIED/INFORMED

CLINICAL DATAPOOL INTERNATIONAL & PE 05.05.95
PATIENT NO.: 928747 SERIAL NO.: 1 PAT. INITIALS:

SEX: _____
AGE: _____
HEIGHT (CM): _____
HEIGHT (KG): _____
MALE YEAR(S)
55
175

DATE RECEIVED BY BAYER: _____
PROFESSION: _____
RACE: _____

2ND SGT INCREASED
SGPT increased
MAY 5, 1992

POSSIBLE
DRUG DISCONT. PERMANE.
IMPROV.
NOT APPLIC.
NO
YES (EXPECTED)

1ST SGT INCREASED
SGPT increased
MAY 5, 1992

POSSIBLE
DRUG DISCONT. PERMANE.
REVERS.
NOT APPLIC.
NO
YES (EXPECTED)

ADVERSE REACTION:
COSTART RECODE:
DATE FROM:
DATE TO:
DURATION OF ADR:
TYPE TO ONSET:
RELATIONSHIP TO DRUG:
CRITERION MEASURE:
OUTCOME:
DID REACT. REAPP. A. REINTROD.:
DID REACT. REAPP. A. REINTROD.:
SERIOUSNESS (AMS):
MOST SERIOUS EVENT (AMS):
REASON FOR SERIOUSNESS (AMS):
LABELLED (0-VERSION):

CONTINUED

PATIENT NO.: 920715 SERIAL NO.: 1 (CONT.)

FURTHER DETAILS OF EVENTS:
HOSPITALIZED FOR ACUTE ARRHYTHMIA AND
WORSENING MYOCARD. INSUFF. WITH PULMONARY
CONGESTION (DATE UNKNOWN) DURING HOSPIT.
DETERIORATION OF DIABETES MELL. BILIRUBIN
TEMPORAL. INCREASED LATER LIVER ENZYMES
INCREASED. COAGULATION DECREASED.

DEATH DUE TO OTHER CAUSES: _____

RELEVANT TEST/LAB DATA:
ON ADMISSION INCREASED HB (15.3) AND HK
(64X). REGULAR LIVER ENZYMES AND
COAGULATION PARAMETERS.

INDICATION FOR USE: _____

DIABETES MELLITUS
MYOCARDIAL INSUFFICIENCY, WORSENING
CONGESTION, PULMONARY
MORBUS PARKINSON
ARRHYTHMIA ABSOLUTA, ACUTE
SCLEROSIS, CEREBROVASCULAR
SCLEROSIS, CARDIOVASCULAR

TREATMENT:

GLUCOBAY (ACARBOSE)
NOVODIOL
OSYROL 100 LASIX
MAGOPAR
DEPUT-H-INSULIN

FORMULATION: DAILY DOSE:

TABLET
3X 1 TAB
1X 0.2 MG
1X 1
2X 125 MG
36+16 IE

RISK FACTOR: _____
REACTION FACTORS: _____
INITIAL REPORTER: _____
15-DAY-REPORT: _____
REPORT TYPE: _____
WHICH AUTHORITY WAS INFORMED: _____

DIET (12 BU)

?
NO
INITIAL
AMK D. AE
BGA
MILES USA
BAYER UK
BAYER I
112665
92003413
GERMANY (D)

ANK-NO.: _____
BOA-NO.: _____
BAYER ORIGIN NO.: _____
COUNTRY: _____
LITERATURE REFERENCE: _____
TITLE: _____
PHARMLINE NO.: _____
REPORT SOURCE: _____
DATE: _____

HEALTH PROFESSIONAL
BOA
JUL 6, 1992

OUTCOME COMMENTS:
AFTER WITHDRAWAL OF GLUCOBAY LIVER
SYN-HESE LEVELS RECOVERED.
PAT. S. DIABETES IS DIFFICULT TO MANAGE.
HIS BLOOD: ACUTE POSTAL/SEPTAL FIBROSIS/
CIRRHOSIS.

CIOMS II COMMENTS:
HEART FAILURE WITH CONGESTION IN THE
LIVER

APPLICATION: DRAL
DRAL
DRAL
DRAL
DATE FROM: MAR 25, 1992
DATE TO: _____
DURATION: CA. 3 MONTHS
CONTINUOUS
CONTINUOUS
CONTINUOUS

CLINICAL DATAPool INTERNATIONAL & PE 05.05.95

PATIENT NO.: 920715 SERIAL NO.: 1 PAT. INITIALS:

SEX: _____ MALE
AGE: _____ 62 YEAR(S)
HEIGHT (CM): _____ 172
WEIGHT (KG): _____ 61

DATE RECEIVED BY BAYER: _____ JUL 3, 1992
PROFESSION: _____ PENSIONER
RACE: _____

ADVERSE REACTION: 1ST TRANSAMINASES INCREASED
COSTARTY DECODE: Liver function test abnormal
DATE FROM: MAR 13, 1992
DATE TO: MAR 25, 1992
DURATION OF ADR: 13 DAYS
RELATIONSHIP TO DRUG: INSUFF. EVIDENCE
COUNTER MEASURE: DRUG DISCONT. PERMANE.
OUTCOME: IMPROV.
DID REACT REAPP. A. REINTROD.: NOT APPLIC.
SERIOUSNESS (AMS): YES
MOST SERIOUS EVENT (AMS): YES
REASON FOR SERIOUSNESS(AMS): YES (EXPECTED)
(LABELLED (O-VERSION)).

CONTINUED

PATIENT NO.: 920699 SERIAL NO.: 1 (CONT)

FURTHER DETAILS OF EVENTS:
DIARRHEA FREQUENCY INCREASED WHILE ON
GLUCOBAY THERAPY PAT. PSYCHIC REMARKABLE
WITH SUSPECTED ALCOHOL ABUSE, SUFFERS
SINCE LONG FROM DIARRHEA. - GLUCOBAY WAS
ADDED TO OTHER UNCHANGED DIABET. THERAPY
BECAUSE OF MISSING EFFICACY.

DEATH DUE TO OTHER CAUSES.

RELEVANT TEST/LAB. DATA:
SGOT 94 U/L; SGPT 291 U/L; GAMMA-GT 683
U/L. HEPATITIS TEST: NEG; A/HEP C NEGATIV

INDICATION FOR USE:
CONCOMITANT DISEASE:
DIABETES
DIARRHEA, RECURRENT
HYPERTENSION
ENTEROPATHIA, DIABETIC, SUSPECTED
PSYCHIC DISTENTION

TREATMENT:
GLUCOBAY (ACARBOSE)
DIABINASE
TENERETIC
LINDIUM (LOPERAMIDE)
OPTIPEN
XANAX (ALPRAZOLAM)
HALCION

FORMULATION, DAILY DOSE:
TABLET 5X100 MG
TABLET 2X100 MG
TABLET 1 TAB
CAPSULE 1-2 CAP
1-2X 600
1-2X 0.5
0.25

RISK FACTOR:
REACTION FACTOR:
INITIAL REPORTER: DTT, R. DR.

REPORT TYPE:
WHICH AUTHORITY HAS INFORMED:
ALCOHOL ABUSE SUSPECTED

AUTHORITY NO.:
BGA-NO.:
BAYER ORIGIN NO.:
COUNTRY:
LITERATURE REFERENCE:
TITLE:
PHARM. LINE NO.:
REPORT SOURCE:
DATE:

INITIAL
CH: SAMZ
CIOMS
MILES USA
BAYER UK
BAYER CH
300/92
92018570
SWITZERLAND (CH)
HEALTH PROFESSIONAL
BAYER CH
JUN 26, 1992

OUTCOME COMMENTS:
TREATMENT STILL ONGOING; TRANSAMINASE
VALUES TURNED TO NORMAL, GAMMA-GT
IMPROVED.

CIOMS II COMMENTS:

APPLICATION: ORAL
ORAL
ORAL
ORAL
ORAL
DATE FROM: FEB 28, 1992
DATE TO:
DURATION: CONTINUOUS
CONTINUOUS
LONG-TERM
BY NEED, YEARS
LONG-TERM

TELEPHONE NO.: 061/721-5353

NOTIFIED/INFORMED

CLINICAL DATAPOOL INTERNATIONAL & PE 05.05.95
PATIENT NO.: 921699 SERIAL NO.: 1 PAT. INITIALS:

SEX: FEMALE
AGE: 66 YEAR(S)
HEIGHT (CM):
WEIGHT (KG):

DATE RECEIVED BY BAYER: JUN 23, 1992
PROFESSION:
RACE:

ADVERSE REACTION: 1ST DIARRHEA WORSENING
COSTART DECODE: Diarrhoe
DATE FROM: MAY 8, 1992
DATE TO:
DURATION OF ADR:
TIME TO ONSET:
RELATIONSHIP TO DRUG:
COUNTER MEASURE:
OUTCOME: POSSIBLE
DID REACT REAPP. A. REINTROD.: NONE
SERIOUSNESS (AMS): REVERS.
MOST SERIOUS EVENT (AMS): NOT APPLIC.
REASON FOR SERIOUSNESS(AMS): NO
LABELLED (0-VERSION): YES (EXPECTED)

ADVERSE REACTION: 3RD SOPT INCREASED
COSTART DECODE: SOPT increased
DATE FROM: MAY 1992
DATE TO: MAY 22, 1992
DURATION OF ADR:
TIME TO ONSET:
RELATIONSHIP TO DRUG:
COUNTER MEASURE:
OUTCOME: UNLIKELY
DID REACT REAPP. A. REINTROD.: NONE
SERIOUSNESS (AMS): REVERS.
MOST SERIOUS EVENT (AMS): NOT APPLIC.
REASON FOR SERIOUSNESS(AMS): NO
LABELLED (0-VERSION): YES (EXPECTED)

ADVERSE REACTION: 2ND SOPT INCREASED
COSTART DECODE: SOPT increased
DATE FROM: MAY 1992
DATE TO: MAY 22, 1992
DURATION OF ADR:
TIME TO ONSET:
RELATIONSHIP TO DRUG:
COUNTER MEASURE:
OUTCOME: UNLIKELY
DID REACT REAPP. A. REINTROD.: NONE
SERIOUSNESS (AMS): REVERS.
MOST SERIOUS EVENT (AMS): NOT APPLIC.
REASON FOR SERIOUSNESS(AMS): NO
LABELLED (0-VERSION): YES (EXPECTED)

ADVERSE REACTION: 4TH GAMMA-GT INCREASE
COSTART DECODE: Gamma-GT increased
DATE FROM: MAY 1992
DATE TO:
DURATION OF ADR:
TIME TO ONSET:
RELATIONSHIP TO DRUG:
COUNTER MEASURE:
OUTCOME: UNLIKELY
DID REACT REAPP. A. REINTROD.: NONE
SERIOUSNESS (AMS): REVERS.
MOST SERIOUS EVENT (AMS): NOT APPLIC.
REASON FOR SERIOUSNESS(AMS): NO
LABELLED (0-VERSION): YES (EXPECTED)

CONTINUE

PATIENT NO.: 911385 SERIAL NO.: 1 (CCNT.)

FURTHER DETAILS OF EVENTS:
PT WITH ELEVATED Y-GT ALREADY BEFORE
GLUCOBAY STARTED. 4.3.91 GLUCOBAY STARTED
FOR ELEVATED BLOOD GLUCOSE. 18.4. OASTRO-
INTEST. COMPL. SINCE TAKING GLUCOBAY (PT
COMM.). DOSE REDUCED TO 150PO/D....

DEATH DUE TO OTHER CAUSES: _____

RELEVANT TEST/LAB. DATA:
1989.1.91. S/91.14. 30.5. 11.6 GAMMA-GT
37.41.58.112.98.48.16. 30.5. 11.6 ALK.P.
136.117.88 (ALAT 103 NORM. 8 (ASAT 176) NORM
13.16.5.91 BLOOD GLUCOSE TEST/30.5.8.000
GLUCOSE 6.6 (NORM).

INDICATION FOR USE: _____
CONCOMITANT DISEASE: _____

TREATMENT:
GLUCOBAY (ACARBOSE)
LITHIUM
NOZIMAN
PROPRIMAL (DEPAQUINE)

RISK FACTOR: _____
RISK FACTOR: _____
RISK FACTOR: _____
RISK FACTOR: _____
REACTION FACTORS: _____
INITIAL REPORTER: _____
REPORT TYPE: _____
WHICH AUTHORITY WAS INFORMED: _____

BOA-NO.: _____
BAYER ORIGIN NO.: _____
COUNTRY: _____
LITERATURE REFERENCE: _____
TITLE: _____
PHARMACY NO.: _____
REPORT SOURCE: _____
DATE: _____

OUTCOME COMMENTS:
2.5 UNCHANGED COMPL. (DIARRHEA, CRAMPS).
WEIGHT LOSS. GLUCOBAY STOPPED. 13.5.91
MORE GASTROINTEST. COMPLAINTS. 30.5. BLOOD
GLUCOSE NORMAL. GAMMA-GT STILL ELEVATED.
LITHIUM+NOZIMAN INDUCE SAME REACTION.

CIDMS II COMMENTS:

GLUCOSE LEVEL ELEVATED SLIGHTLY
DEPRESSIVE MANIC ILLNESS

FORMULATION: DAILY DOSE:
3X100 MG
100 MG
25-50 MG

SMOKER
ALCOHOL ABUSUS
DIABETES MELLITUS. MILD
DIABETES DIET
CONCOMITANT DRUG SUSPECTED
REININGO, J. H.A.
INITIAL
CIDMS
BAYER NL
92005658
NETHERLAND (NL)

APPLICATION: ORAL
ORAL
ORAL
DATE FROM: MAR 4, 1991
DATE TO: MAY 2, 1991
DURATION: 60 DAYS
CONTINUOUS
CONTINUOUS
DEC 1990

HEALTH PROFESSIONAL
NOV 17, 1991

PATIENT NO.: 911365 SERIAL NO.: 1 (CONT.)

ADVERSE REACTION: 7TH ASAT INCREASED
COSTART DECODE: S00T increased
DATE FROM: MAY 14, 1991
DATE TO: MAY 30, 1991
DURATION OF ADP: 17 DAYS
TIME TO ONSET: INSUFF. EVIDENCE
RELATIONSHIP TO DRUG: REVERS.
COUNTER MEASURE: NOT APPLIC.
OUTCOME:
DID REACT REAPP. A. REINTROD.:
SERIOUSNESS (AMS):
MOST SERIOUS EVENT (AMS):
REASON FOR SERIOUSNESS (AMS):
LABELLED (0-VERSION):

CONTINUED

NOTIFIED/INFORMED

CLINICAL DATAPool INTERNATIONAL & PE 05.05.95
PATIENT NO.: 911385 SERIAL NO.: 1 PAT INITIALS:
SEX: _____ AGE: _____
HEIGHT (CM): _____ MALE YEARS: _____
WEIGHT (KG): _____ 165
175

IMTE RECEIVED BY BAYER: _____ NOV 11, 1991
PROFESSION: _____ UNEMPLOYED
RACE: _____ CAUCASIAN (WHITE)

2ND SPASM, BOMEL
Abdominal pain
APR 18, 1991
MAY 13, 1991
26 DAYS
POSSIBLE
DRUG DISCONT. PERMANE.
REVERS.
NOT APPLIC.

4TH ALC. PHOSPHATASES INCREASED
Alkaline phosphatase increased
MAY 16, 1991
JUN 11, 1991
29 DAYS
INSUFF. EVIDENCE
REVERS.
NOT APPLIC.

6TH ALAT INCREASED (SOPT)
SOPT increased
MAY 16, 1991
MAY 30, 1991
17 DAYS
INSUFF. EVIDENCE
REVERS.
NOT APPLIC.

DIARRHEA
Diarrhea
APR 18, 1991
MAY 13, 1991
26 DAYS
POSSIBLE
DRUG DISCONT. PERMANE.
REVERS.
NOT APPLIC.

BURBORYGMI
Flatulence
APR 18, 1991
MAY 13, 1991
26 DAYS
POSSIBLE
DRUG DISCONT. PERMANE.
REVERS.
NOT APPLIC.

GAMMA-GT INCREASED MORSEMED
Gamma-GT increased
MAY 14, 1991
CONTINUED
INSUFF. EVIDENCE
REVERS.
NOT APPLIC.

15'
ADVERSE REACTION:
COSTARTY DECODE:
DATE FROM:
DATE TO:
DURATION OF ADR:
TIME TO ONSET:
RELATIONSHIP TO DRUG:
COUNTER MEASURE:
OUTCOME:
DID REACT REAPP. A. REINTROD.:
SERIOUSNESS (AMS):
MOST SERIOUS EVENT (AMS):
REASON FOR SERIOUSNESS(AMS):
LABELLED (O-VERSION):

3RD
ADVERSE REACTION:
COSTARTY DECODE:
DATE FROM:
DATE TO:
DURATION OF ADR:
TIME TO ONSET:
RELATIONSHIP TO DRUG:
COUNTER MEASURE:
OUTCOME:
DID REACT REAPP. A. REINTROD.:
SERIOUSNESS (AMS):
MOST SERIOUS EVENT (AMS):
REASON FOR SERIOUSNESS(AMS):
LABELLED (O-VERSION):

5TH
ADVERSE REACTION:
COSTARTY DECODE:
DATE FROM:
DATE TO:
DURATION OF ADR:
TIME TO ONSET:
RELATIONSHIP TO DRUG:
COUNTER MEASURE:
OUTCOME:
DID REACT REAPP. A. REINTROD.:
SERIOUSNESS (AMS):
MOST SERIOUS EVENT (AMS):
REASON FOR SERIOUSNESS(AMS):
LABELLED (O-VERSION):

CONTINUED

PATIENT NO.: 910545 SERIAL NO.: 1 (CONT.)

FURTHER DETAILS OF EVENTS:
REACTION (WHITE STOOLS, DARK URINE) MAP-
PENED OVER A WEEKEND.

DEATH DUE TO OTHER CAUSES: _____

RELEVANT TEST/LAB DATA:
84.12.90; GAMMA-OI 12, ALK. PHOSPH. 126.

INDICATION FOR USE: _____
CONCOMITANT DISEASE: _____
DIABETES MELLITUS
HEART INSUFFICIENCY
CORONARY HEART DISEASE
DIVERTICULOSIS

TREATMENT: _____
GLUCOBAY (ACARBOSE) 100 MG TAB 3X100 MG
SPEC. DIAGN. OR OTHER MEASURES: _____
REACTION FACTORS: _____
INITIAL REPORTER: _____
FORMULATION: DAILY DOSE:
CHOLECYSTECTOMY, CONDITION AFTER
STRASSBURG, R. DR.

15-DAY-REPORT: _____
REPORT TYPE: _____
WHICH AUTHORITY HAS INFORMED: _____
NO INITIAL
BGA
AMK P. AE
91901436
BUYER ORIGIN NO.: _____
COUNTRY: _____
LITERATURE REFERENCE: _____
TITLE: _____
PARALLEL NO.: _____
REPORT SOURCE: _____
HEALTH PROFESSIONAL
SALES REPRESENTAT.
APR 3, 1991

DATE: _____

OUTCOME COMMENTS:
REACTION DISAPPEARED COMPLETELY AFTER
WITHDRAWAL OF DRUG REACTION LASTED ONLY
2 DAYS (PAT.'S COMMENT): NO LAB-TESTS, PAY
WAS SEEN BY THE PHYSICIAN 1 WEEK LATER.
PAT HAS HAD CHOLECYSTECTOMY.

CIOMS II COMMENTS:

APPLICATION: _____ DATE FROM: _____ DATE TO: _____ DURATION: _____
ORAL NOV 1990 DEC 1, 1990 CA 1/2 MTM

TELEPHONE NO.: 08351/7221

CLINICAL DATAPOOL INTERNATIONAL & PE 05.05.95

NOTIFIED/INFORMED

PATIENT NO.: 918545 SERIAL NO.: 1 PAT. INITIALS:

SEX: FEMALE
AGE: 70 YEAR(S)
HEIGHT (CM): 170
WEIGHT (KG): 74

DATE RECEIVED BY: BAYER
PROFESSION: HOUSEWIFE
RACE: CAUCASIAN (WHITE)

ADVERSE REACTION: 1ST CHOLESTASIS
COSTART DECODE: Cholestatic jaundice
DATE FROM: NOV 30, 1990
DATE TO: DEC 4, 1990
DURATION OF ADR: 5 DAYS
TIME TO ONSET: UNLIKELY
RELATIONSHIP TO DRUG: DRUG DISCONT. PERMANE.
COUNTER MEASURE: REVERS.
OUTCOME: NOT APPLIC.
DID REACT. REAPP. A. REINTROD.:
SERIOUSNESS (AMS):
MOST SERIOUS EVENT (AMS):
REASON FOR SERIOUSNESS(AMS):
LABELLED (D-VERSION):

CONTINUED

May 30, 1995

3

COSTART term	Bayer Germany Control No.	Bayer West Haven Control No.	3-Day or 10-Day FDA Safety Report
Bilirubinemia (n=1)	931157	B94013	No
Jaundice (n=2)	940501*	B94047	No
	950158	B95013	10-Day
Increased lactic dehydrogenase (n=1)	921431*	Not Assigned	-

* Indicates cases in which patients had multiple events involving the liver.

May 30, 1995

2

COSTART term	Bayer Germany Control No.	Bayer West Haven Control No.	3-Day or 10-Day FDA Safety Report
Increased SGOT (n=5)	911385*	B92045	No
	920699*	B92088	No
	920747*	Not Assigned	-
	930094*	Not Assigned	-
	932298*	Not Assigned	-
Increased gamma-GT (n=6)	911385*	B92045	No
	920699*	B92088	No
	921431*	Not Assigned	-
	930093*	Not Assigned	-
	930168	Not Assigned	-
	941831	Not Assigned	-
Increased alkaline phosphatase (n=2)	911385*	B92045	No
	921431*	Not Assigned	-
Cholestatic jaundice (n=3)	910545	Not Assigned	-
	921205	Not Assigned	-
	950714	B95046	10-Day

* Indicates cases in which patients had multiple events involving the liver.

May 30, 1995

1

Acarbose
International Spontaneous Reports Involving the Liver

COSTART term	Bayer Germany Control No.	Bayer West Haven Control No.	3-Day or 10-Day FDA Safety Report
Abnormal liver function tests (n=10)	920715	B92090	10-Day
	920986	Not Assigned	-
	921426	Not Assigned	-
	930326	Not Assigned	-
	930327	B93024	No
	940009	B94003	No
	940501*	B94047	No
	941480	Not Assigned	-
	950022	Not Assigned	-
	950518	B95038	No
Aggravation reaction (worsening transaminase increase) (n=1)	820257	B92035	No
Increased SGPT (n=6)	911385*	B92045	No
	920898*	B92088	No
	920747*	Not Assigned	-
	930093*	Not Assigned	-
	930094*	Not Assigned	-
	932298*	Not Assigned	-

* Indicates cases in which patients had multiple events involving the liver.

**Medical Officer's Review of a
New Drug Application**

1. Title and General Information

NDA No: 20-482

Submission date: September 6, 1994

Generic Name: Acarbose

Proposed Trade Name: Precose®

Chemical Name: O-4,6-dideoxy-4-[[[(1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]- α -D-glucopyranosyl-(1-4)-O- α -D-glucopyranosyl-(1-4)-D-glucose

Sponsor: Miles Inc.
Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516

Pharmacologic Category: Alpha-glucosidase inhibitor

Proposed Indication(s): Non-Insulin Dependent Diabetes Mellitus
Monotherapy or as adjunctive with sulfonylureas

Dosage Form(s) and Routes of Administration: 50, 100. mg Tablets
Oral Administration

NDA Drug Classification: S

Related Drugs: None

Related Reviews:

Statistical Review Dated: 3/14/95

Biopharm dated: 6/9/95

NDA 20086: 5/21/91

I Background

II Review of Clinical Studies

006/052	obese patients
008/054	tolbutamide study
91/006	dose response
007/051	sulfonylurea study
620	German fixed dose study
626	Canadian adjunct study
633	European dose-response study
025	safety study
0642	Italian monotherapy study
0619	metformin study
87/009	insulin study
0583	Czech study
summary of the use of acarbose with other antidiabetic agents	

III Dose-Response Relationship

IV Review of Safety and Tolerability

V Assessment of Overall Risk/Benefit Relationship

VI Recommendations for labeling

VII Information to Be Sought in Post-Approval Period

VIII Summary and recommendations

I. Background

The original IND for acarbose was filed in 1980. Clinical studies were later halted because of pre-clinical findings. An Endocrine and Metabolic Advisory Committee meeting was held in 1982 to consider the significance of increased incidence of renal tumors associated with therapy in a two year rat study. Additional carcinogenicity studies were suggested, and following their completion and resolution of this issue in 1985, clinical studies resumed in the US. In the meantime, Acarbose was approved first in Czechoslovakia in 1987 and has been marketed extensively throughout Europe and elsewhere. It is estimated that approximately _____ patients have been treated with acarbose since it was first introduced.

An NDA was submitted for the indication of improved glycemic control in both non-insulin dependent diabetes (NIDDM) in August, 1990. The E&M Advisory Committee considered the NDA in July, 1991 and recommended non-approval. The following issues were raised as a basis for the Committee's decision:

- (1) Questionable clinical significance of the modest improvements in glycemic control.
- (2) Lack of dose-response data and, specifically, identification of the lowest average dose that results in maximal response.
- (3) Unknown consequences of long term alterations in the intestinal environment
- (4) Concerns about systemic effects of the drug, particularly as a liver toxin, and possibly as an inhibitor of intracellular enzymatic activity.
- (5) The possibility that transaminase elevations seen in controlled studies could presage cumulative hepatocellular disease during chronic use.

The sponsor subsequently withdrew the NDA, but completed a one year safety study that had been initiated prior to the NDA submission. Dose response studies conducted in the US and Europe have also since been completed along with a special GI study. These studies provide additional evidence that the sponsor hopes will satisfactorily address the concerns raised by the previous advisory committee. After the sponsor withdrew the NDA, it also made a decision based on equivocal results of the two studies conducted and submitted to the original the NDA that only an indication confined to NIDDM patients would be pursued.

This review will deal primarily with the issues raised at the last E&M Advisory hearing for acarbose and the information that has become available since that meeting.. The results of all pivotal studies will be reviewed with special focus on the problems raised by the previous Advisory Committee. Attached as an appendix is a summary document prepared by the sponsor that contains descriptive information and the sponsor's conclusions.

II. Review of clinical studies

The pivotal studies are summarized in the following table:

Study Number	Location	Study Design and Indication	Number of Patients on acarbose
D86-006/052	U.S.	Acarbose vs placebo as monotherapy in the treatment of obese NIDDM patients inadequately controlled by diet alone	91
D86-008/054	U.S.	Comparison of acarbose, tolbutamide, acarbose plus tolbutamide, to placebo in NIDDM patients inadequately controlled by diet alone	134
D91-006	U.S.	Dose response study comparing 100 mg, 200 mg, and 300 mg acarbose TID to placebo as monotherapy in NIDDM patients inadequately controlled by diet alone	165
D86-007/051	U.S.	Acarbose vs placebo in combination with maximal sulfonylurea therapy in NIDDM	71
620	Germany	Acarbose 100mg tid vs placebo as monotherapy in the treatment of obese NIDDM patients	47
626	Canada	Acarbose vs placebo within four stratified groups of NIDDM patients (background therapy of diet alone, sulfonylurea, metformin, or insulin)	172
633	5 European Countries	Dose response study comparing 25mg, 50mg, 100mg, 200mg acarbose tid to placebo as monotherapy in NIDDM patients	438
025	U.S.	Safety study of acarbose 50-300 mg tid vs placebo	240
642	Italy	Dose response study comparing 50mg and 100mg acarbose tid to placebo as monotherapy in NIDDM patients	41

0619	France	Acarbose at 50mg and 100mg vs placebo in patients on metformin	88
009	U.S.	Acarbose 50-300 mg tid in NIDDM patients on insulin	107
0583	Czechoslovakia	acarbose 50-300 mg tid in NIDDM patients on insulin	29
Total			1623

D86-006/052 - Obese patients

The placebo group consisted of 98 patients and the acarbose group 91 patients. Roughly half of the patients were male, 60% Caucasian, 25% black and 13% Hispanic. The mean age was 56 years with a duration of diabetes of about 5 1/2 years and a starting HbA1c of 6.7%. The initial dose of acarbose was 50 mg tid which was increased up to 300 mg tid. At the end of the 24 week study, acarbose was superior to placebo for HbA1c and for all plasma glucose measurements. Hemoglobin A1c rose 0.53% in the placebo group but fell 0.06 in the acarbose group. ($p < .0001$). The mean 120 min postprandial glucose rose 12.45 mg% in the placebo group but fell 37.95 mg% in the acarbose group. Similar changes were observed for the other postprandial glucose measurements. Fasting plasma glucose rose 10.53 in the placebo group but fell 5.11 in the acarbose group. No significant changes were seen in body weight or serum lipids.

There was a higher incidence of reporting of adverse events in the acarbose group than in the placebo group. For flatulence this was 58% vs 25%, for diarrhea this was 22% vs 10% and for abdominal pain this was 19% vs 6%. Five patients in the acarbose group developed abnormally low hemoglobin value which returned to normal in 4 and was felt not to be drug related. 4% of acarbose patients developed elevated SGOT(1% of placebo patients) while 9% developed elevated SGPT(2% of placebo patients). In one patient the rise in transaminase level was felt to be serious by the investigator. Elevations returned to normal in all cases after the drug was discontinued. One patient on acarbose was reported to have had a severe hypoglycemic reaction.

Conclusion:

Acarbose improved hyperglycemia and reduced hemoglobin A1c in obese diabetics, but was associated with a high incidence of flatulence, diarrhea and abdominal pain. These gastrointestinal complaints are troublesome to patients but are not dangerous. Of more concern, is that some patients developed increased SGOT and SGPT levels. However these elevations

returned to normal when the drug was discontinued. These results show that acarbose is a safe way to reduce HbA1c levels in obese diabetics.

D-008/054 Tolbutamide Study

The purpose of this study was to compare acarbose to tolbutamide alone and tolbutamide plus acarbose in NIDDM patients. There were four treatment groups. Patients in the acarbose group received 200 mg acarbose tid. Patients in the tolbutamide group received tolbutamide tid starting with 250 mg and increasing the tolbutamide dose in order to bring the 1 hr postprandial plasma glucose to less than 200 mg%. Patients in the combined therapy group received 200 mg tid of acarbose, and tolbutamide starting at 250 mg tid and increasing the dose of tolbutamide in order to achieve a 1 hr postprandial glucose of less than 200 mg%. There was a placebo control group as well which received no active drug. The duration of treatment with active drug was 24 weeks. This was preceded by a 6 week placebo run-in period and followed by a 6 week washout. The primary efficacy variable was the change in baseline in Hb A1c. Changes in glucose, insulin, and lipid levels were also studied. Each group consisted of 59-65 patients with a mean age of 56 years and a mean duration of diabetes of 5.1 to 5.6 years. There were fewer males (39%) in the acarbose group than in the other groups (52- 56%). Approximately 50% were Caucasian, 25% black and 25 % Hispanic. The four groups had mean baseline fasting plasma glucose of 214-227 mg% and mean baseline HbA1c of 6.73-7.1 %. The results of treatment are shown in figure 1.

HbA1c increased by a mean of 0.04 in the placebo group but fell by 0.54 in the acarbose group, 0.93 in the tolbutamide group and 1.32 in the combined treatment group. These differences were all statistically different. However, no difference existed among the treatment groups in the percent of patients who had a favorable response as defined as a HbA1c fall of 1. The percent responders was 8% in the placebo group, 17% in the acarbose group, 25% in the tolbutamide group and 24% in the combined treatment group. Plasma glucose levels decreased in all three treatment groups. As with HbA1c, tolbutamide was more effective than acarbose, but the combination was more effective than either tolbutamide or acarbose alone. Acarbose also partially blocked the rise in serum insulin levels and increase in body weight that was observed with tolbutamide alone. The final average daily dose of tolbutamide was significantly lower in patients on acarbose than in those on tolbutamide alone(649 mg vs 794 mg tid). No significant treatment effects were seen on serum cholesterol, triglyceride or HDL.

There was a higher reporting of adverse events in patients taking acarbose. 80% in the acarbose group and 77% in the combined treatment group reported flatulence compared to 35% in the placebo group and 34% in the tolbutamide group. For diarrhea the reporting was 27% in the acarbose group, 35% in the combined treatment group, and 6 % in the tolbutamide and placebo groups. One patient in the acarbose group and two patients in the combined treatment groups

developed elevations in transaminase levels greater than 80% above the upper limit of normal.

Conclusion:

Tolbutamide was more effective than acarbose (200 mg tid) in reducing HbA1c levels and plasma glucose levels, but the combination of tolbutamide plus acarbose was superior to either drug alone. The dose of tolbutamide required to achieve a 1 hr postprandial glucose of less than 200 mg% was lower in patients who were also taking acarbose. Acarbose also partially blocked the rise in serum insulin and increase in body weight that occurred with tolbutamide alone. There was increased reporting of flatulence and diarrhea in patients on acarbose but no serious adverse events. This study supports the combination of acarbose and tolbutamide in patients with NIADDM, and shows that acarbose lowers the dose of tolbutamide while achieving even better glycemic control. It may also be of importance that addition of acarbose to tolbutamide partially blocked the weight gain and rise in insulin levels observed with tolbutamide alone, in view of the evidence that hyperinsulinemia itself may contribute to the development of vascular disease. As would be expected, the incidence of hypoglycemia was greater in the groups that achieved better glycemic control, 6% in the placebo group, 9% in the acarbose group, 17% in the tolbutamide group and 25% in the combined treatment group.

D91/006 Dose-Response study

This was a placebo- controlled, double blind dose response study for acarbose in patients with NIDDM inadequately controlled by diet alone. There was a four week placebo run-in period after which acarbose was started at 100 mg tid. The dose was increased to 200 mg tid after two weeks, and again to 300 mg tid after two weeks. The final four dosing groups consisted of acarbose 100 gm tid, 200 mg tid and 300 mg tid and placebo. Patients were on their final dosing schedule for 12 weeks. The primary efficacy variable was HbA1c which was considered to be the best indicator of glycemic control. Response criteria were as follows: Responder A HbA1c <7 and a reduction from baseline of at least 0.5%; Responder B criteria for Responder A or HbA1c reduction from baseline of at least 1%. Secondary efficacy measures were plasma glucose levels in association with a meal tolerance test, Insulin and lipid levels were also followed. The final groups consisted of 64 placebo patients, 58 patients on acarbose 100 mg tid, 54 patients on 200 mg tid and 53 patients on 300 mg tid.

With respect to hemoglobin A1c all three doses of acarbose were superior to placebo ($P < .0002$). However, none of the acarbose groups differed significantly from each other. The magnitude of the treatment effect was 0.78, 0.73, and 1.10 for 100, 200, and 300mg tid respectively. An A Response (HbA1c <7.0 and reduction of 0.5), was 8% for placebo, 16% for acarbose 100 mg tid and 11% for acarbose 200mg and 300 mg tid. A B response(HbA1c of <7.0 and reduction of 0.5 or reduction of 1.0) was 11% for placebo, 33 % for 100mg acarbose, 26% for 200 mg acarbose and 40% for 300 mg acarbose tid.

Gastrointestinal complains were more frequent in patients taking acarbose than placebo. 23% of placebo patients complained of flatulence, compared to 78%, 87%, and 79% for 100 mg, 200 mg, and 300 mg tid of acarbose respctively. 10% of placebo patients complained of diarrhea compared to 33%, 32%, and 36% for the acarbose groups. 5% of placebo patients complained of abdominal pain compared to 18%, 15% and 19% of acarbose patients. Elevations in SGPT and SGOT greater than three times the upper limit of normal occured in three patients on 200 mg and 300 mg acarbose but did not occur in the patients on placebo or on 100 mg tid acarbose.

Conclusion:

Acarbose lowers mean HbA1c levels and causes a favorable response (reduction of >1.0 or to <7.0) in a substantial number of patients, but there was no clear dose- response relationship over the range of treatment doses that were used. By contrast a three fold increase in hepatic transaminases was seen in some patients on 200mg tid of acarbose but not at 100 mg tid. Thus, the data do not support a maximal dose in excess of 100 mg tid.

007/051 Sulfonylurea study

This is a double blind placebo- controlled trial on the effect of acarbose in patients with NIADDM who are not adequately controlled on maximal doses of sulfonylurea. The study consisted of a 6 week pretreatment period, a 24 week double blind parallel treatment period (acarbose vs placebo) and a 6 week follow-up period. Enrollment criteria included a diagnosis of NIDDM for at least 6 months, stable weight for at least 3 months, and a fasting plasma glucose > 140 while on a maximal dose of a sulfonylurea. Approximately 48% of the patients were glyburide (20mg), 29% of glipizide (40mg), 13% on chlorpropamide (750mg), 10% tolazimide (1000mg) and 1% tolbutamide (3000mg). Efficacy criteria were Hb A1c, and glucose and insulin levels after a standard meal tolerance test.. The dose of acarbose was titrated from 50 mg tid up to 300 mg tid based on therapeutic response or downward based on tolerance. There were 71 patients in the acarbose group and 70 in the placebo group.

Acarbose was significantly superior to placebo for hemoglobin A1c ($p < .01$) which rose by 0.18 in the placebo group and fell by 0.23 in the acarbose group, and for all plasma glucose variables except fasting glucose. Serum insulin levels were also significantly lower in the acarbose group. Body weight and serum lipid levels were not affected.

14% of patients in the acarbose group discontinued the medication because of adverse events compared to 5% in the placebo group. The incidence of any body system adverse event was significantly greater in the acarbose group (70%) vs the placebo group (41%). Most of the adverse events occurred in the gastrointestinal system. The occurrence of each event for acarbose vs placebo was as follows: flatulence 67% vs 30%, diarrhea 30% vs 4%, abdominal pain 17% vs 6%. 11% of acarbose patients had an abnormally high SGPT level compared to 2% of placebo patients. In all instances where follow-up information was available, the transaminase level returned to normal after discontinuation of acarbose. There were no deaths in this study. One placebo patient had a cerebrovascular accident. One acarbose patient had a cardiac arrest 18 days after the drug had been discontinued. He was successfully cardioverted.

Conclusion:

The study shows that acarbose is effective in reducing HgbA1c levels and postprandial hyperglycemia in patients who are on maximal doses of sulfonylurea. That this was accomplished at lower insulin levels may be of importance in view of body of evidence which suggests that hyperinsulinemia itself may contribute to the macrovascular complications of NIADDM. The data support the sponsor's claim that acarbose may be used in combination with sulfonylureas. The requirement that patients be on the maximal recommended doses of sulfonylureas was a particularly stringent and important criterion, because the results of the study show that the effects of acarbose were clearly additive to the preexisting effect of the

sulfonylurea.

620 German fixed dose study

This was a double blind, placebo-controlled randomized comparison of acarbose 100 mg tid to placebo in patients with NIDDM who were not controlled on diet alone and had not previously been treated with insulin or oral hypoglycemic agent. Following a 4 week diet alone run-in period patients were randomized to acarbose 100 mg tid or placebo. Treatment lasted for 24 weeks. Primary efficacy variables were Hb A1 (which is slightly higher than A1c) and 1 hour postprandial glucose. There were 47 patients in each study arm with a mean age of 59 years and a mean duration of diabetes about 4.8 (placebo) and 6.5 (acarbose) years. All patients were Caucasian. Prior to treatment the mean Hb A1 was 9.3 % in the acarbose group and 9.4 % in the placebo group. Mean 1 hr postprandial blood glucose was 255 mg/dl and 258 mg/dl respectively.

Acarbose was superior to placebo in reducing Hb A1 levels($p=.003$) The reduction of HbA1 was 0.11 in the placebo group and 0.62 in the acarbose group. Mean 1hr postprandial glucose went from 258 mg/dl to 243 in the placebo group and from 255 to 189 in the acarbose group. 48 % of the acarbose patients reported flatulence during the study compared to 28% of the placebo patients. However, the flatulence subsided over the course of the study. In the first 4 weeks, 14 of 47 acarbose patients reported flatulence described as severe, 16 reported moderate flatulence and 6 reported slight flatulence. By the end of 24 weeks, only 5 reported moderate flatulence and 11 reported slight flatulence.

Conclusion: This study supports the effectiveness of acarbose in reducing HbA levels and postprandial glucose in previously untreated diabetic patients. Flatulence was a frequent complaint. The reporting of the severity of the flatulence decreased over the course of the study but it is not clear if this represented a quantitative decrease in the amount of flatus or just that the patient had become accustomed to it.

0626 Canadian Adjunct Study

This was a four arm, double blind trial to compare the effect of acarbose vs placebo as adjunct therapy in patients with NIDDM. The four treatment strata were diet alone, diet plus insulin, diet plus metformin, and diet plus a sulfonylurea (of which 95% were on glyburide). The purpose of the study was to determine if addition of acarbose to existing therapy would improve control which had previously been felt to be inadequate. After a six week run in period patients were treated with placebo or acarbose for 52 weeks. The initial dose of acarbose was 50 mg tid which was increased as tolerated and required to improve glycemic control as judged by the treating physician. The primary efficacy variables were changes from baseline in HbA1c and plasma glucose AUC after a standard meal tolerance test. Clinically relevant response criteria were defined as follows: Responder 1 was HbA1c <7 and/or absolute decrease of at least 1 unit. Responder 2 was HbA1c <7 and/or a decrease of at least 15% from baseline. Each study arm consisted of 38-52 patients, details of demographics are shown in the table. The mean age was 56-59 years. Mean duration of diabetes was about 5.2 years in the diet alone patients to about 12.5 years in the insulin treated patients. Mean starting HbA1c was about 6.7% in patients on diet alone, 7.7% in patients on insulin, 7.8% in patients on metformin, and 8.0 in patients on sulfonylurea.

After 12 months of treatment, all acarbose treated groups showed a mean fall of HbA1c while all placebo treated groups showed a slight increase, except the insulin group in which there was a slight decrease. Acarbose was superior to placebo in all groups except insulin where the acarbose treatment effect was only of borderline significance ($p=0.8$). This appeared to be due to the improvement in HbA1c observed in the insulin-placebo group but not the other placebo groups. The acarbose treatment effect (mean change in HbA1c) was 0.8 in the metformin group ($p=.01$), 0.9 in the diet alone group ($p=.005$), 0.9 in the sulfonylurea group ($p=.002$) and 0.4 in the insulin group ($p=0.8$). A time course of the change in HbA1c is shown in figure 2.

As measured by change in postprandial AUC glucose, acarbose was superior to placebo in all groups including the insulin group, with a p value of 0.01 in the metformin group, 0.004 in the insulin group, and <0.0001 in the diet alone and sulfonylurea groups. The percent of patients who "responded" as defined by a HbA1c <7 and/or absolute fall of 1.0 was approximately doubled by acarbose in all groups except the insulin treatment group. For diet alone there were 60% responders with acarbose and 30% with placebo ($p=0.02$). For metformin there were 61% responders with acarbose and 26% with placebo ($p=0.005$). For sulfonylurea there were 55% responders with acarbose and 25% with placebo ($p=0.004$), but for insulin there were 51% responders with acarbose and 41% with placebo ($p=0.37$).

As expected from others studies, all acarbose groups had more adverse events related to the gastrointestinal tract than the placebo group. For instance, for patients on diet alone flatulence

was reported in 74 % of acarbose patients and 41% of placebo patients. Diarrhea was reported in 45% of acarbose patients and 13% in placebo patients. Abdominal cramps was 26% in acarbose patients and 13% in placebo patients. The same effect of acarbose was reported in the other three treatment groups as well. More acarbose patients developed increase liver transaminase levels than placebo patients. A rise in SGPT of greater than 1.8% the upper limit of normal was reported in 105 of acarbose patients and 55 of placebo patients. Acarbose patients had less serious adverse events, but the numbers were small. In the sulfonylurea patients, 7 serious events, including one death, were reported in the placebo patients but none in the acarbose patients. In patients on insulin, there were 7 serious events in placebo patients and two in the acarbose patients. Other than one case of hypoglycemia in an insulin-treated patient, none of the other serious events were directly related to treatment of hyperglycemia.

Conclusion:

Acarbose clearly improved glycemic control in patients on diet alone, sulfonylurea or metformin. A marginal improvement was observed in insulin treated patients as well. A high frequency of gastrointestinal complaints was observed in the acarbose treated patients. However, acarbose, if anything, appeared to decrease the incidence of severe adverse events in patient on insulin or sulfonylureas. The incidence of elevated liver enzymes with acarbose was less in this study than in others. The results of this study support the use of acarbose in combination with metformin and sulfonylureas, and perhaps with insulin.

0633 European Dose-Response study

This was a large double blind dose-response study of acarbose as monotherapy in patients with NIADDM. Following a six week run-in period patients received a fixed dose of acarbose at doses of 25, 50, 100 and 200 mg tid or placebo. The treatment lasted for 24 weeks. The primary efficacy variable was change in HgbA1c. Each study group consisted of 103-113 patients with a mean age of 57-60 years and duration of diabetes of 2.0-2.4 years. Mean HgbA1c rose in the placebo group (0.31) but declined in all the acarbose groups. The decline was 0.13 at 25 mg tid, 0.44 at 50 mg tid, 0.18 at 100 mg tid and 0.71 mg 200 mg tid. . The treatment effect (change in HbA1c with acarbose minus placebo) was therefore 0.44 at 25 mg tid, 0.75 at 50 mg tid, 0.49 at 100 mg tid and 1.02 at 200 mg tid. Thus a clear dose response relationship was not observed above 50 mg tid . Exploratory pairwise comparisons demonstrated significant differences between the 200 mg group and the 25 and 100 mg group ($p < 0.05$) , but not between the 50mg and 200 mg tid groups. As expected there was a high incidence of gastrointestinal complaints in the acarbose groups. 20% of placebo patients reported flatulence compared to 37% at 25 mg, 47% at 50mg, 47% at 100 mg and 60% at 200mg tid. The reporting of flatulence decreased with time in all groups. For placebo patients, 53% reported flatulence at weeks 4-8 but only 26% at weeks 20-24. Among placebo patients 13% reported flatulence at weeks 4-8 but only 5% at weeks 20-24. Increased liver transaminase were less often reported in this study than in other studies. An increased SGOT was observed in 5% of placebo patients, 2% at 25mg, 6% at 50mg, 7% at 100 mg and 10% at 200 mg tid of acarbose. SGPT elevation was in 2% of placebo 25mg and 50mg patients, 3% at 100 mg and 5% at 200 mg tid acarbose.

Conclusion:

In this study, the maximum therapeutic effect of acarbose was observed at 50 mg tid. The effect of 200 mg tid was not statistically greater than 50 mg tid. Reporting of flatulence diminished over the course of the study in both the acarbose patients and the placebo patients. Thus it is not clear if the amount of flatus in the acarbose patients actually decreased over time (as might be expected from compensatory enzyme induction in the distal small bowel) or if the patients were just less likely to report the flatulence. The decreased reporting among placebo patients suggests the latter explanation.

NDA 20482
PRECOSE

2 OF 3

D-025 Safety Study

This was a multi-center placebo controlled trial to examine the safety of acarbose in NIDDM and IDDM. One patient was randomized to placebo for every two to acarbose. The 56 week double blind treatment period included an eight week titration period during which 50mg, 100mg, 200mg, 300mg acarbose were each given for two weeks with an step up in dose every two weeks as tolerated (the 300 mg dose was discontinued 11 months into the study because of increased transaminases). This step-up titration phase was followed by a 48 week maintenance phase during which time patients were maintained on their maximum tolerated dose. Patients were permitted to continue prior antidiabetic drugs and concomitant antidiabetic agents could be added or their dosage adjusted during the course of the study. The study groups consisted of 240 patients on acarbose and 119 on placebo. Specialized gastrointestinal studies were done at one Center in 21 patients. 21% of the patients had IDDM and 70% had NIDDM. 51% of patients were male. In the acarbose group 75% were Caucasian, 14% black, and 11% Hispanic. In the placebo group 76% were Caucasian, 8% black and 13 % Hispanic.

Acarbose was superior to placebo with respect to HbA_{1c}; however the importance of this difference was hard to interpret because changes in other antidiabetic drugs was permitted. 20% of the acarbose treated patients withdrew from the study because of adverse events compared to 5% of the placebo patients. Acarbose -treated patients showed higher incidence of flatulence and diarrhea than placebo treated patients. These symptoms decreased over time in patients who continued the treatment. A greater incidence of low calcium levels was seen in the acarbose patients(28% vs 16) but in 98 % of cases the lower calcium level was transient and returned to normal despite continuation of acarbose treatment. There was a greater incidence of low Vitamin B6 levels in the acarbose group compared to placebo (33% v 23%) but the level returned to normal in 68% of the acarbose treated patients despite continuation of therapy. There were no symptoms associated with this change.

There was a greater incidence of treatment emergent elevation in SGPT(31% vs 16%) and SGOT(17% vs 11%) in the acarbose group than in the placebo group. For enzyme elevations greater than 3 times the upper limit of normal, SGPT elevation was observed in 9% of acarbose patients compared to 1% of placebo treated patients;. SGOT elevation was observed in 2% of acarbose patients compared to 0% of placebo patients. These elevated transaminase levels decreased rapidly after the drug was stopped and was not associated with any signs or symptoms of hepatic disease. The transaminase rise appeared to be dose- dependent. No patient on a maximum acarbose dose of 100 mg tid had a rise in SGPT or SGOT exceeding 1.8 times the upper limit of normal. Plasma acarbose-related activity(sucrase inhibition assay) was higher in patients with elevated transaminase activity than in patients without elevated transaminase

activity.

Special studies were performed in two centers (St Lukes Roosevelt Hospital, New York City - Dr Pi-Sunyer, and Minneapolis Veterans Administration Hospital, Dr Niehwoehner) to evaluate the possible effect of acarbose on colonic factors. 27 patients were studied at St Lukes-Roosevelt and 18 at the Minneapolis VA. A total of 15 patients received placebo and 30 received acarbose. The purpose of the study was to determine the effect of chronic acarbose administration upon fecal water, calories, fat, and nitrogen excretion, fecal pH and changes in short chain fatty acids. Changes in the metabolism of colonic bacteria was sought by measuring changes in breath hydrogen production and in the fecal concentration of two bacterial strains that may be functionally important, digoxin metabolizing bacteria and diacylglycerol producing bacteria. Changes in cell proliferation was sought using material obtain by rectal biopsy.

Acarbose treated patients had an increase in fecal weight compared to controls and a decrease in fecal pH. There was no difference in fecal excretion of fat or nitrogen; however colonic butyrate, as well as acetate and propionate were increased in the acarbose-treated patients. This may be of significance because short chain fatty acids, particularly butyrate, have been considered important metabolic components for the health of the human colon. Indeed colonic butyrate is believed to be the principal fuel for colonocyte metabolism. Breath hydrogen output was increased in acarbose-treated patients reflecting bacterial metabolism in the colon of carbohydrate that was not absorbed in the small intestine. Histologic examination of colonic crypts did not show any evidence of hyperplasia resulting from acarbose treatment, nor did tritiated thymidine incorporation show any change in cell proliferation. There was also no evidence of loss of digoxin or diacylglycerol metabolizing enzymes.

Conclusion:

This 56 week study was performed to evaluate the long term safety of acarbose. As expected from its mechanism of action, the drug caused a high incidence of flatulence and diarrhea. However the frequency of these events decreased over time. A reversible rise in SGPT and SGOT were also observed at higher doses of acarbose. Acarbose related activity was higher in plasma of patients with elevated transaminases than in other patients. There were no reports of clinically significant liver disease. Previous concerns about possible harmful long term effects of acarbose on colonic function were not borne out. The higher levels of some short chain fatty acids, particularly butyrate, in acarbose-treated patients might actually be expected to be beneficial to colonic health.

Study 0642 - Italian monotherapy study

This was a placebo controlled double blind study at two centers in Italy of placebo vs acarbose 50mg tid and acarbose 100mg tid in NIDDM who had previously been inadequately treated with diet alone. There was a four week placebo run-in period after which patients were randomized to placebo vs acarbose 50 mg tid vs acarbose 100 mg tid. Treatment last for 16 weeks thereafter. There were 23 patients in the placebo group (16 men, and 7 women) with a mean age of 55.5 years. The 50 mg tid acarbose group consisted of 18 patients (10 men and 8 women) with a mean age of 58.9 years. The 100 mg tid acarbose group consisted of 23 patients(15 men and 8 women) with a mean age of 53.8 years. In the placebo group, HbA1c went from 7.22 at the beginning of the study to 7.39 at the end. In the acarbose 50 mg tid group, HbA1c went from 7.07% to 6.51 %. In the 100 mg tid acarbose group HbA1c went from 7.15 % to 6.36 %. These differences between acarbose and placebo were highly significant ($p < 0.0001$) at both doses. However, the difference between the 50 mg tid and the 100 mg tid was not significant($p = 0.57$). Mean plasma glucose(area under the curve after a standard meal) were also reduced by acarbose in both doses ($p < 0.01$).

The overall incidence of adverse events was 31% in the placebo group, 32 % in the 50 mg tid acarbose group, and 63 % in the 100 mg tid group. The most common complaint, flatulence occurred in 24% of placebo patients, 29% at 50 mg tid and 52% at 100 mg tid of acarbose. The difference between 100 mg and placebo was statistically significance ($p = 0.032$) Gastrointestinal symptoms caused treatment to be discontinued in one placebo patient, two 50 mg and two 100 mg acarbose patients. Increased SGPT was observed in 1 placebo patient, two 50 mg, and two 100 mg acarbose patients.

Conclusion:

This small study shows confirms that acarbose at doses of 50 mg tid and 100 mg tid was safe and effective in NIDDM patients previously treated with diet alone. No statistically significant difference was observed between the two doses. Gastrointestinal complains were the major side effects

0619- Metformin Study

This double blind study was conducted in France to examine the effect of acarbose in NIDDM patients treated with diet alone or diet with other oral agent(s). The data were submitted in this NDA to support the indication for acarbose to be used in combination with metformin. Males and females were studied aged 35-70. Therapy was initiated with acarbose 50 mg tid for six weeks or placebo. After that, they were given acarbose 100 mg tid or placebo for the remainder of the trial if fasting blood glucose was greater than 140 mg/dl and two hour postprandial glucose was greater than 200 mg/dl. The duration of treatment was six months.

Of 183 patients, 88 were randomized to acarbose and 95 to placebo. Of patients valid for efficacy analysis there were 65 on acarbose and 82 on placebo. Acarbose-treated patients had a mean fall of HbA1c of 0.69 compared to a fall of 0.24 in placebo group ($p=0.014$). Acarbose patients had a mean fall in 2 hr postprandial glucose of 26.1 mg/dl compared to a mean rise of 7.02 in the placebo group ($p<0.001$). As found in other studies, acarbose caused greater gastrointestinal complaints than placebo. 53.4 % of acarbose patients complained of flatulence compared to 11.6% of placebo patients. Diarrhea was 25% of acarbose patients and 6.3% of placebo patients. Abdominal pain was 17% of acarbose patients and 13.7 % of placebo patients. Increases in liver enzymes were observed to the same extent in both groups.

Among patients on metformin, 13 received acarbose and 12 received placebo. The dose of metformin was not given. In the placebo group HbA1c rose by 0.48%. In acarbose patients, HbA1c fell by 0.27%. Thus there was a mean treatment effect of 0.75 ($p=0.1498$)

Conclusion:

The treatment effect of acarbose when added to patients taking metformin was a fall in HbA1c of 0.75; however the change was not statistically different from placebo. Since this change is similar to the effect seen in study 626, it seems likely that failure to achieve statistical significance was due to the small sample size.

D87-009 Insulin Study

This is a double blind placebo controlled study in patients with NIDDM who were being treated with insulin. There was a six week pretreatment period followed by a 24 week parallel control study followed by a 6 week post-treatment period. The initial dose of acarbose of 50 mg tid was increased to 100, 200, and 300 mg tid at six week intervals as tolerated and required for control of postprandial hyperglycemia. To avoid hypoglycemia, investigators were encouraged to lower the dose of insulin when the study medication was initiated or the dose increased. Changes in HbA1c, postprandial blood glucose, insulin dose and frequency of hypoglycemia were followed as measures of efficacy. The study group consisted of 54% men and 46% women, mean age 59 years. 71% were white. The study was performed at seven centers. The study groups consisted of 110 randomized to placebo and 107 randomized to acarbose.

Acarbose was superior to placebo with respect to HbA1c and all measures of blood glucose. HbA1c (in %) fell 0.17 in the placebo group and 0.57 in the acarbose group ($p=0.0001$). Mean fasting glucose rose 11.87 mg/dl in placebo patients but fell 4.55 mg/dl in acarbose patients. 120 min postprandial glucose rose 6.03 mg/dl in placebo patients but fell 44.16 mg/dl in acarbose patients. There was also a small but statistically significant decrease in insulin dose in acarbose-treated patients. Mean insulin dose rose 1.19% in the placebo group but fell 7.14% in the acarbose group ($p=0.0015$). There was no difference in the number of hypoglycemic episodes.

Conclusion:

Acarbose improves glycemic control in insulin-treated patients with NIDDM while decreasing the amount of insulin used.

5421/0583 Czech Study

This was a placebo-controlled randomized study of the effects of acarbose in patients with NIDDM who were being treated with insulin. After a 4 week pretreatment period, patients were hospitalized for one week during which time they received acarbose or placebo in addition to their insulin. The acarbose treatment was continued for 23 weeks and followed by a four week follow-up period. The starting dose of 50 mg tid was increased to 100 mg tid 200 mg and 300 mg tid at two week intervals as tolerated. The insulin dose remained the same. The placebo group consisted of 21 women and 9 men. The acarbose group consisted of 18 women and 11 men. The median age was 62 years. The median duration of diabetes 10 years, and the median duration of insulin treatment was 4 years 2 months.

Mean HbA1c went from 9.1% to 7.7% in acarbose patients and 9.6% to 8.5% in placebo patients for a mean treatment effect of 0.3 (p=0.003). Fasting glucose went up slightly in the placebo group (12.3 mg/dl to 13.2 mg/dl) but was unchanged in the acarbose group (11.1 mg/dl). It is claimed that this difference was statistically significant (p=0.044). The results section says that the duration of treatment was 24 months but the methods section says 24 weeks. The results section says that the insulin dose went down in 16 acarbose patients compared to 9 placebo patients (p=.006) but this is inconsistent with the earlier statement in methods that insulin dose was to remain the same.

Conclusion:

This study claims to support the effectiveness of acarbose in insulin-treated patients, but the magnitude of the treatment effect is very small. Also, I am not convinced that the groups were really matched because the mean fasting glucose and HbA1c were both lower at baseline in the acarbose group than in the placebo group. The authors claim that the treatment effect was highly significant (although small) but do not comment on the differences in baseline data. The report also contains other troublesome inconsistencies. I am reluctant to accept the results of this study without an independent statistical report and review of the primary data.

Summary of the use of Acarbose with other Antidiabetic Drugs

Sulfonylureas:

The efficacy of acarbose used in combination with sulfonylureas is shown by three well controlled studies. Particularly impressive are the results of study 007/051 in which acarbose was shown to improve glycemic control in patients taking maximal doses of sulfonylureas. This study shows convincingly that acarbose adds a degree of control which sulfonylureas alone cannot. Furthermore, improved control occurs at a lower dose of sulfonylurea and with lower insulin levels. Although the experience with tolazimide and chlorpropamide in controlled trials is small, it seems unlikely that these drugs behave differently from the other sulfonylureas. Therefore, the data support a general statement that acarbose is effective in patients on sulfonylureas, and may be beneficial in patients in whom sulfonylureas alone do not provide adequate control..

Metformin:

The major claim for efficacy of acarbose in metformin-treated patients comes from study 626 (the Canadian study) in which 42 patients on metformin were given acarbose with a treatment effect(HbA1c reduction) of 0.8 ($p=0.01$). Study 0619 showed a treatment effect of 0.75 but this was not statistically significant , perhaps because the number of patients was so small (13 on acarbose and 12 on placebo). Also, we do not know what the effect of increasing the metformin dose would have been. Therefore we do not know that acarbose adds something which metformin alone could not. This is different from the situation with the sulfonylureas. Finally, there is a paper in the literature which reports to show that acarbose decreases the bioavailability of metformin in normal subjects (Eur J.Clin Invest 1994 Aug 24 Suppl 3: 50-54)

Insulin:

There are three studies in the NDA which are claimed to support the concomitant use of insulin with acarbose. In study 0626(the Canadian adjunct study) , acarbose failed to show a statistically significant improvement in control in patients on insulin, although it did improve control in patients on sulfonylureas, metformin and diet alone. It should be noted that patients in the insulin- placebo group experienced an improvement in control, over the course of the study which was not observed in the other placebo groups. Also, there was a beneficial trend in the insulin- treated patients even though it was not statistically significance. The drug effect of acarbose in insulin -treated patients was a mean fall of HbA1c of 0.4 . This is exactly the same treatment effect as that in study 87/009 which was highly significant. This study consisted of 107 acarbose-treated patients, 110 on insulin plus placebo, and showed a beneficial effect of

acarbose on glucose levels in addition to hemoglobin A. The drug was also associated with an mean 8% reduction in the insulin dose used but was not associated with a change in hypoglycemic episodes. The third study (5421/0583), the Czech study) is also reported to show a small but significant effect of acarbose on reducing HbA1c in insulin-treated patients. But the report contains many inconsistencies and therefore cannot be used to support a claim of efficacy at present.

Recommendation:

The data in the NDA support a claim for the use of acarbose in combination with sulfonylureas. The labeling should allow a statement to the effect that patients who are inadequately treated with sulfonylureas alone may benefit from the addition of acarbose. The data suggesting that acarbose may be beneficial in patients on metformin or insulin are not convincing. Approval of these indication should not be given until the advisory committee has had the opportunity to review the data and make recommendations. In the meanwhile, the sponsor should be encouraged to do post-marketing studies which may provide data to support these indications.

III DOSE -RESPONSE RELATIONSHIP

Subsequent to withdrawal of the NDA in 1991, the sponsor has put much effort into trying to define the dose-response relationship for acarbose. The present data do not clearly establish at what dose of acarbose the maximal drug effect is ordinarily obtained. However, a clear dose response relationship is seen with respect to the drug's most worrisome adverse reaction, elevations in SGPT and SGOT. This point must be born in mind so as not to get bogged down in a debate about uncertainties in the dose response relationship, which cannot be resolved with the information that is currently available. The most important consideration is to establish a dose range in which acarbose can be used safely. Despite lingering uncertainties about the possibility of greater efficacy at higher doses, the data clearly show that 100 mg tid is the maximal dose that one can use safely. Pushing the dose beyond this range leads to an unacceptable risk of the development of abnormal liver function tests. It is a moot point whether pushing the dose beyond this level leads to somewhat more efficacy or not. Indeed, the data in this application do not even show that 100 mg tid is more effective than 50 mg tid. One should bear these "bottom line" considerations in mind when considering the data presented in the following paragraphs.

Acarbose is always given three times a day with the first bite of each meal. The dose range of 25mg to 300 mg tid has been studied. The 300 mg dose was discontinued because of increased transaminases, but it is still useful to look at the effectiveness of this dose versus lower doses. Data from D91-006 show that 300 mg tid had a treatment effect (reduction of HbA1c vs placebo) of 1.10, compared to 0.78 for 100 tid and 0.73 for 200 mg tid. These differences were not significantly different, nor was the response rate based on HbA1c, although the 300 mg dose did lower 1 hr postprandial glucose and glucose AUC measurement significantly more than did the 100 mg tid dose. The data therefore suggest, but do not clearly establish, that 300 mg tid is more effective than lower doses.

As mentioned earlier, the 300 mg tid dose was eliminated because of the risk of hepatic toxicity. When one considers the remaining doses, there is no evidence that increasing the dose above 50 mg tid improves efficacy. One problem with the dose-response data is an unexplained decrease in treatment effect of 100 mg tid vs 50 mg tid in study 633 (see figure 3). However, even in Study 642 where the two doses were directly compared there was no significant difference between 50 mg and 100 mg tid. When all the dose-response data are considered (as shown in the attached table), there is no evidence that the doses above 50 mg tid have any greater efficacy. Unfortunately, all of these data were obtained from studies using parallel treatment arms. What is needed is a study in which patients are treated with 50 mg tid long enough to observe a maximum treatment effect before raising the dose to 100 mg tid. Based on what Dr Lebovitz told the advisory committee, there is a compensatory increase in glucosidase activity in the distal small bowel in response to acarbose treatment, which may account for the decrease in complaints of flatulence after several months of treatment. If this is so, one would expect that increasing the dose after several months might offset this compensatory increase in enzyme

activity and lead to greater efficacy. Until this type of study is done, we cannot be sure that 100 mg tid of acarbose is more effective than 50 mg tid.

IV REVIEW OF SAFETY AND TOLERABILITY

All studies of acarbose have disclosed a high incidence of gastrointestinal complaints to be associated with the drug. These symptoms and expected consequences of the drug's mechanism of action and arise from the delivery of undigested carbohydrate to the distal intestine with subsequent gas production by the action of intestinal bacteria. In the pool of placebo controlled trials performed in the United States, the incidence of flatulence, diarrhea and abdominal pain was 77%, 33%, and 21% in the acarbose-treated patients compared to 32%, 12% and 9% in the placebo-treated patients. The frequency of gastrointestinal complaints was greatest at the beginning of treatment and decreased after several months of treatment. The high frequency of gastrointestinal complaints at the beginning of treatment accounted for the greater number of patients who terminated the treatment because of side effects among acarbose-treated patients (17%) than among placebo treated patients (5%). Although the gastrointestinal effects were dose related, there was still a high incidence of complaints even in the lower dose range. In the European dose-response study (0633) for instance, reporting of flatulence was as follows: 20% in placebo patients, 37% at 25 mg, 47% at 50mg, 47% at 100 mg, and 60 % at 200 mg tid.

Although the gastrointestinal effects may limit the acceptability of acarbose to many patients, they are self-limiting and do not pose any danger to health. Of potentially greater significance is the increase in SGOT and SGPT which has been observed in acarbose-treated patients. In placebo controlled trials conducted in the United States, increased transaminase levels was observed in 15% of patients on acarbose compared to 7% of placebo patients. This effect was dose related. At 50 mg tid and 100 mg tid the incidence of increased transaminase levels was the same in acarbose patients as in placebo patients. However at 200 mg tid, the incidence was double that in placebo patients. Increased SGPT levels exceeding three times the normal level occurred in 3 % of patients on 200 mg tid acarbose and 1% of patients on placebo. The elevated transaminase levels in these studies was asymptomatic and returned to normal after the drug was discontinued. Indeed, there were several patients in whom the elevated transaminase levels returned to normal even when the drug was inadvertently not discontinued.

Spontaneous Reports of Increased Transaminases with Acarbose (only cases with SGPT > 3x on Acarbose 300mg or less)

3/23/95	300 mg	SGOT 924 SGPT 1190	resolved
5/17/95	300mg	SGOT 1938 SGPT 2350 alk phos 359, bili 11.4	resolved
2/2/95	300mg	SGPT 295	resolved
11/25/92	150mg	SGOT 101 SGPT 156	resolved
1/26/92	300mg	SGOT 94 SGPT 291	?
11/12/91	300mg	SGOT 103 SGPT 174	?

The risk of increased transaminase levels should not prevent acarbose from being marketed provided that the dosing is appropriate. The question remains: is there a dose of acarbose which is completely safe? Placebo controlled trials have shown no statistically significant increase in transaminase levels if the dose is 300 mg (100 mg tid) or less. On the other hand, there are six spontaneously reported cases even at the lower doses in which the SGPT exceeded three times the normal range (see table), including two patients in whom the SGPT exceeded 1000. Thus even at 300 mg there still must be concern about the potential for acarbose to cause liver injury, even recognizing that these data came from uncontrolled reports.

The mechanism by which acarbose may lead to increased transaminase levels is not known. Less than 2% of the active drug is absorbed, although about 35% of radiolabeled acarbose is absorbed as mostly inactive products of bacterial degradation. One study has shown that acarbose bioactivity was higher in blood of patients with increased transaminase levels than those with normal transaminase levels. This observation raises the possibility that liver injury may be due to active drug. It has been reported (J Biochem, Tokyo 1990, Feb; 107(2): 197-211) that intraperitoneal injection of 400 mg/kg of acarbose into rats caused accumulation of liver glycogen in a histological pattern similar to that observed in type 2 glycogen storage disease (Pompe's disease). The dose given to rats to produce this effect however was 5,000 times the amount absorbed from an oral dose in man of 300mg/70kg (assuming 2% absorption). There is no evidence from animal studies that either acarbose or its metabolites are hepatotoxic in the dose range used clinically. It is possible that indirect effects of the drug such as changes in bacterial flora or in the composition of nutrients in the gut could cause the effect on hepatic enzyme levels. All these possible explanations are highly speculative at present and it is not likely that this question will be answered in the foreseeable future. Regardless of the mechanism however, it must be borne in mind that increased transaminase levels in acarbose-treated patients is reversible and dose-dependent. Despite extensive clinical experience we have no reports of disability related to acarbose treatment. None of the acarbose patients in the placebo controlled trials developed symptomatic liver disease. There are two spontaneous reports of clinically significant liver disease which may have been related to acarbose, but both of these patients recovered after the drug was withdrawn.

Finally we must consider the effects of acarbose on the intestinal environment. This was an issue of concern to the 1991 Advisory Committee. The sponsor performed sophisticated studies on the colonic environment of patients who had been on acarbose for one year. These studies included breath tests and biopsy. The findings of increased stool weight and hydrogen production were expected from the drug's mechanism of action. The major unexpected finding from this study was increased butyric acid in the colon of acarbose treated patients. Since butyric acid is believed to be a major source of nutrients for the colonic cell, this finding would, if anything, be beneficial to colonic health. Of particular importance was that there was no evidence of increased cell proliferation, either by microscopic appearance or thymidine incorporation. Thus there is no evidence to suggest that acarbose may predispose to cancer or an other disease of the

colon. Indeed, Bartram et al.(Cancer Res 1991 Aug 15; 51(16): 4238-42 have suggested that changes in fecal bile acids and neutral sterols produced by acarbose may actually reduce the risk of colon cancer.

V ASSESSMENT OF OVERALL RISK/BENEFIT RELATIONSHIP

The current data shows that treatment with acarbose as monotherapy can be expected to cause a fall of hemoglobin A1c of about 0.8%. Acarbose also improves glycemic control in patients taking sulfonylureas and also appears to prevent the weight gain which often accompanies the use of sulfonylureas. There is a high incidence of annoying side effects such as flatulence and diarrhea, but in most cases these side effects do not cause patients to discontinue treatment. Placebo-controlled trials have failed to show major toxicity provided that the dose does not exceed 100 mg tid., although at higher doses reversible increases in transaminase levels were observed. Worldwide experience (approximately one million patient years) with acarbose has disclosed five reports of SGPT levels greater than three times normal in patients taking 100 mg tid and one patient taking 50 mg tid.

Is the small improvement in glycemic control produced by acarbose of sufficient clinical importance to warrant the use of acarbose either as monotherapy or in combination with other drugs?

With respect to the direct consequences of hyperglycemia itself, such as polyuria, it is unlikely that treatment with acarbose will cause any clinically significant improvement. Furthermore, to the extent that symptoms of hyperglycemia may be diminished, they would be more than offset by the bothersome gastrointestinal symptoms brought on by acarbose itself. The fundamental question which must be answered is whether the improvement in hyperglycemia brought about by acarbose can be expected to decrease the risk of developing the long term complications of diabetes. The DCCT (Diabetes Control and Complications Trial) established that intensive treatment of IDDM patients with insulin, aimed at bringing hemoglobin A1c down to a near normal level, resulted in decreased risk of the development (or worsening) of retinopathy, neuropathy and nephropathy (N Engl J Med 1993; 329: 977-86). The results of the DCCT are consistent with other similar intervention trials (N Engl J Med 1995; 332: 1305-6) and suggests that it would be desirable to lower hemoglobin A1c as much as possible were it not for the development of hypoglycemia. The risk of hypoglycemia severe enough to require the intervention of another person was three fold greater in patients receiving intensive insulin treatment than in those receiving conventional treatment. The incidence of hypoglycemia severe enough to require the intervention of another person was nearly one episode per patient per year in the intensively treated group. Thus the risk of hypoglycemia must be weighed in all patients before intensive treatment can be recommended. The DCCT did not address whether it was necessary to get the hemoglobin A1c to near normal levels (with the concomitant hypoglycemia) in order to achieve improvement in the risk of complications. However a more recent study has shown that the development of nephropathy and retinopathy is substantially less in patients whose hemoglobin A1c was less than 8.1% than in patients with higher levels, but that a hemoglobin A1c level lower than 8.1 seemed to confer little additional benefit (see attached figure). These data give rise to the concept of a threshold of hyper-glycemia above

which the risk of complications is substantially increased. If this concept turns out to be correct it would establish a goal for all diabetic patients to achieve a hemoglobin A1c level of 8.1. More intensive treatment (and the risk of hypoglycemia) to achieve a near normal level of hemoglobin A1c may be justified in certain patients but not in all (N Engl J Med 1995; 332: 1251-5).

It is in this context in which the potential use of acarbose should be considered. Acarbose is much less effective in decreasing hemoglobin A1C than are insulin or the sulfonylureas. However hypoglycemia is not observed with acarbose as it is with the more potent agents. The fall in hemoglobin A1c of 0.8 units observed with acarbose is not large but may be worthwhile in certain patients. For instance a decrease in hemoglobin A1c from 8.8% to 8.0% would be accompanied by a roughly 40% decrease in the risk of microalbuminuria according to the data of Krowlewski et al.(see figure 4). If such a reduction could be accomplished without risky or unpleasant side effects, there would little reason not to try. On the other hand, acarbose treatment is associated with a high incidence of unpleasant side-effects. Flatulence and diarrhea are not dangerous but will obviously limit the acceptability of acarbose for many patients.

The only potentially dangerous side effect which is known to occur with acarbose is a rise in liver transaminase levels. As discussed previously we are not aware of any patient in placebo-controlled studies who developed symptomatic liver disease due to acarbose or in whom the transaminase levels did not return to normal after the drug was discontinued. Indeed there were several cases in which the transaminase levels returned to normal spontaneously even though acarbose treatment was inadvertently continued. Finally it must be stressed that the rise in transaminase levels was dose-dependent, and was not observed in patients taking 100 mg tid or less in placebo-controlled trials. However, there are five spontaneous reports of patients taking 100 mg tid who developed SGPT levels greater than 3x normal, including two in whom the SGPT exceeded 1000..

Analysis of the risk/benefit relationship supports the use of acarbose at a dose of 50 mg tid. The flatulence which this drug often produces will limit its acceptability in many patients. However those patients who continue the drug can expect an improvement in glycemic control of about 0.8 % unit in hemoglobin A1c which may help to delay or prevent the development of complications of diabetes. A near maximal effect on lowering hemoglobin A1c can be achieved at a dose of 50 mg tid and there is no increased incidence of elevated liver transaminases. The risk/benefit relationship does not support pushing the dose beyond 100 mg tid. There is little if any improvement in glycemic control when the dose of acarbose is increased to 200 mg tid. However the higher dose is clearly associated with a rise in the levels of liver transaminases. Thus, to push the dose beyond 100mg tid would be to expose the patient to added risk without a reasonable expectation of added benefit and is not justified. What remains uncertain is whether it is justified to increase the dose from 50 mg tid to 100 mg tid. Evidence of increased transaminase levels at 100 mg tid comes from uncontrolled case reports and therefore may not be valid. On the other hand, we have no evidence at present that 100 mg tid is more effective than 50 mg tid.

The simplest way of dealing with this problem is to approve a single dose of 50 mg tid. The data presented in this NDA would certainly justify this stand. On the other hand, such restrictive labeling would be at variance with the way acarbose is used throughout the world and fails to recognize the possibility that certain patients might benefit from the higher dose. Since the risk of increased transaminase levels has not been clearly shown to be higher at 100 mg tid, I am inclined to approve this dose provided that the sponsor agrees to do a post-marketing study to examine the effect of increasing the dose to 100 mg tid in patients who had been on 50 mg tid for several months. Changes in labeling will also need to be made as indicated below.

VI COMMENT ON PROPOSED LABELING

The proposed labeling provides data from four studies of the use of acarbose in NIDDM, three as monotherapy and one in combination with tolbutamide. The data on efficacy and adverse events are clearly presented. The section on Indications and Usage is particularly well done. It stresses the importance of diet and exercise and states that "the use of Precosee must be viewed by both 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". It also explains that data on the importance of reducing hemoglobin A1c levels comes from studies of patients with IDDM not patients with NIDDM, but that it is not unreasonable to assume that patients with NIDDM will derive the same benefit from blood glucose control.

The HbA1c data presented in the table is different from the data presented by the sponsor elsewhere. Also, the tables will need to be revised to reflect the change in maximum dose to 100 mg tid. It is potentially misleading to show efficacy data obtained at doses which exceed the maximum recommended dose. The data are still of interest but an asterisk should indicate that 100 mg tid is the maximum recommended dose.

In the section on titration and maintenance the PI states "The maximum recommended dose is 200 mg three times daily and is recommended when the benefits clearly outweigh the risks." I would argue that there are no instances when the benefits of the 200 mg tid dose clearly outweigh the risks and that this dosage should be deleted. The PI should state that some patients may benefit from increasing the dose from 50 mg to 100 mg tid but that:

there is no clear evidence that 100 mg tid is more effective than 50 mg tid

Increasing the dose above 50 mg tid may add to the risk of increased transaminases

HbA1c and transaminases should be measured 3-6 months after the dose change so that the 50 mg tid dose can be reinstated if the higher dose did not prove more effective, or the drug can be stopped if there is a rise in transaminases

The section dealing with the dose-related rise in liver transaminases should be retained but with the explanation that the 200 mg tid dosage is no longer recommended.

The pivotal study on the concomitant use of acarbose with tolbutamide was done at a acarbose dosage of 200 mg tid. Nevertheless I do not believe that elimination of the 200 mg tid dose would require removing the statement in section 11.3 Indications and Usage that "PRECOSE may also be used in combination with sulfonylurea therapy." However, an asterisk should indicate that the 200 mg tid dose is no longer recommended.

I also question the need for the 100 mg tablet. The standard dose should be 50 mg tid. There is little evidence for a higher dose. There may individual cases in which a physician may wish to try doubling the dose to see if he can obtain better efficacy. But the dose should be reduced back to 50 mg tid if the 100 mg tid dose did not produce better glycemic control. The concept that 50 mg is the standard and 100 mg the exception would be reinforced if only the 50 mg tablet were available.

Although the data in the NDA are not adequate to support a claim that acarbose is indicated for use with insulin, the possibility must be considered that some diabetics on insulin may receive acarbose nonetheless. Therefore, it is appropriate to include a warning for patients on insulin, similar to the warning for patients on sulfonylureas, that addition of acarbose may increase the risk of hypoglycemia.

VII INFORMATION TO BE SOUGHT IN THE POST-APPROVAL PERIOD

Acarbose is indicated as monotherapy in patients with NIDDM and may be used in combination with sulfonylureas. Although the data to support the use of acarbose as monotherapy is very strong, there is relatively little information about its use with other drugs. Once approved it is possible, even likely that clinicians will consider using acarbose for indications for which approval has not been obtained. These potential indications would be in combination with metformin and insulin in NIDDM and with insulin in IDDM. A plan to obtain information in these areas should be discussed as part of the approval process.

The first issue is the concomitant use of acarbose with metformin in NIDDM. In study 626, the adjunct study, acarbose was compared to placebo for concomitant use with sulfonylurea, metformin, and insulin in NIDDM. The additional reduction of hemoglobin A1c brought about by acarbose was 0.9% in patients treated with diet alone ($p = .005$), 0.8% in patients on Metformin ($p = .01$) and 0.9% for patients on sulfonylurea ($p = .002$). A smaller reduction of 0.4% was observed for patients on insulin ($p = .07$). Since the metformin group consisted of only 41 patients, the data are not sufficient to allow approval for concomitant use of acarbose with metformin at the present time. However the sponsor should be encouraged to initiate studies which might develop this indication. Of particular importance would be a study on the effect of addition of acarbose to patients who were on a maximum dose of metformin. Also, the sponsor needs to address the issue of decreased bioavailability of metformin by acarbose.

The second issue is the concomitant use of acarbose with insulin. I think it is likely that clinicians may wish to add acarbose to insulin in an attempt to improve glycemic control in patients with both NIDDM and IDDM. Based on its mechanism of action, one would expect acarbose to be effective in this setting. The data in the NDA which bears on this point directly is from study 87/009 in which acarbose produced small but significant reductions in HBA1c, plasma glucose, and insulin dose in 107 NIDDM patients compared to 110 controls. There was no change in the reported episodes of hypoglycemia, but no information about asymptomatic hypoglycemia was presented.

In study 626 there were 91 insulin treated patients with NIDMM, 41 treated with acarbose and 50 treated with placebo. The difference in the change of hemoglobin A1c was 0.4% which is only about half the effect of acarbose observed in patients on oral agents in the same study, and was of borderline significance ($p < .08$). Acarbose failed also to show a favorable response in insulin treated patients as defined as hemoglobin A1c < 7 and/or decrease of at least 15%. On the other hand, if efficacy had been defined as a decrease in postprandial glucose (AUC - area under the curve following a meal), acarbose would have been as effective in insulin- treated patients as in patients on sulfonylureas or metformin. One possible explanation for this difference is that acarbose may decrease hypoglycemia in insulin treated- patients as much as postprandial hyperglycemia. Although we often think of a fall in hemoglobin A1c as reflecting a

decrease in hyperglycemia, increasing episodes of hypoglycemia will also decrease hemoglobin A1C. Unfortunately, study 626 did not provide data on this point. There is already evidence for a role of acarbose in treating patients with reactive hypoglycemia (Eur J Clin Invest 1994 Aug; 24 Suppl 3:40-44). By delaying glucose absorption, acarbose appears to raise the valleys as well as flattening the peaks of blood glucose. The possibility that acarbose reduces hypoglycemic episodes in diabetic patients on insulin should be pursued.

Diabetic patients take a lot of other medications which may potentially interact with acarbose. Examples that have apparently not been studied yet are thiazide, diuretics, lipid lowering drugs, tricyclic antidepressants and anticonvulsants. Post marketing studies should examine the effects of acarbose on these classes of drugs.

Details of a long term dose response study which should be done in the post-marketing period have been discussed in previous sections.

VIII SUMMARY AND RECOMMENDATION

200 mg dose deleted from 6/27/95 PI. P.I. 7/10/95

The data submitted in this NDA shows that acarbose is safe and effective as monotherapy or in combination with a sulfonylurea in patients with NIDDM at a dose of 50 mg tid.. The claim in the PI that "the maximum recommended dose is 200 mg tid and is recommended when the benefits clearly outweigh the risks " should be rejected. The higher dose exposes patients to the risk of elevated liver transaminases which would require the cost and discomfort of frequent monitoring. No data are presented in the NDA to indicate that 200 mg tid is more effective than 100 mg tid; therefore it is not possible to identify patients in whom the " benefits clearly outweigh the risks". Indeed the use of 100 mg tid dose is questionable and should only be allowed with certain conditions. The sponsor should also be encouraged to do further studies on the concomitant use of acarbose with metformin and insulin.



Robert I Misbin MD
Medical Officer
June 26, 1995

Outstanding review done within few weeks of becoming a medical officer.

*A. Lanning
6/30/95*

Group Leader's Note

While acarbose has modest efficacy, ^{causes} significant amounts of minor GI symptoms, and at high doses can cause liver injury; its overall risk/benefit relationship is probably more favorable than that of sulfonylurea agents. Because of its low potential for systemic effects, particularly cardiovascular, it is reasonable to attribute all the benefits associated with glycemic control in the DCCT to the extent that acarbose improves glycemic control. Thus, in the case of acarbose the benefits and risks are particularly well-defined and acceptable.

G Alexander Fleming MD
Group Leader
June 30, 1995

I have worked closely with Dr. Nybri and agree with all of his analyses and conclusions. He has added substantially to the understanding of this therapy's role and safe use.

A Fleming
6/30/95

Change from Baseline in Efficacy Variables

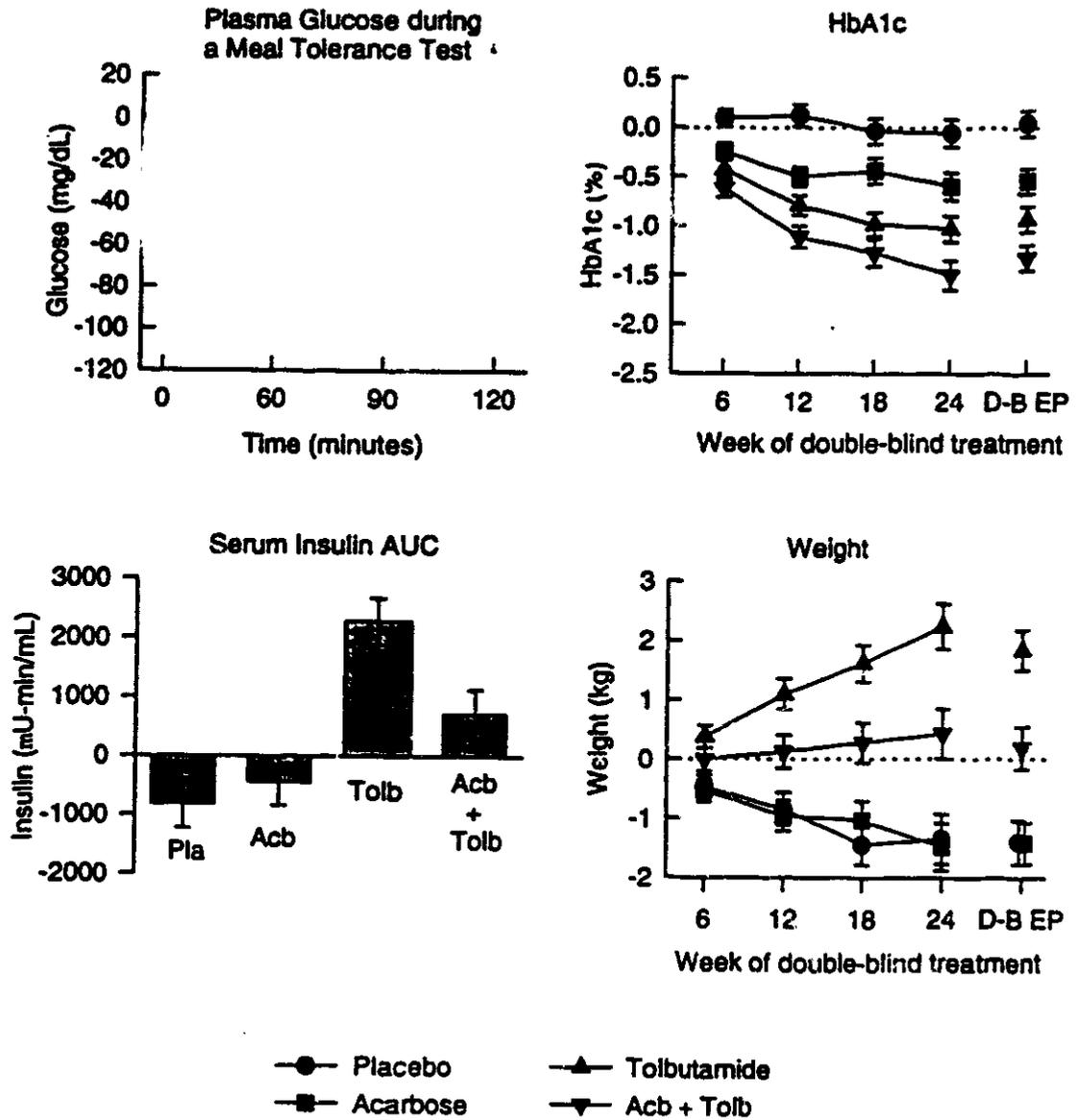


Figure 1

Study 626
Change from Baseline in HbA1c

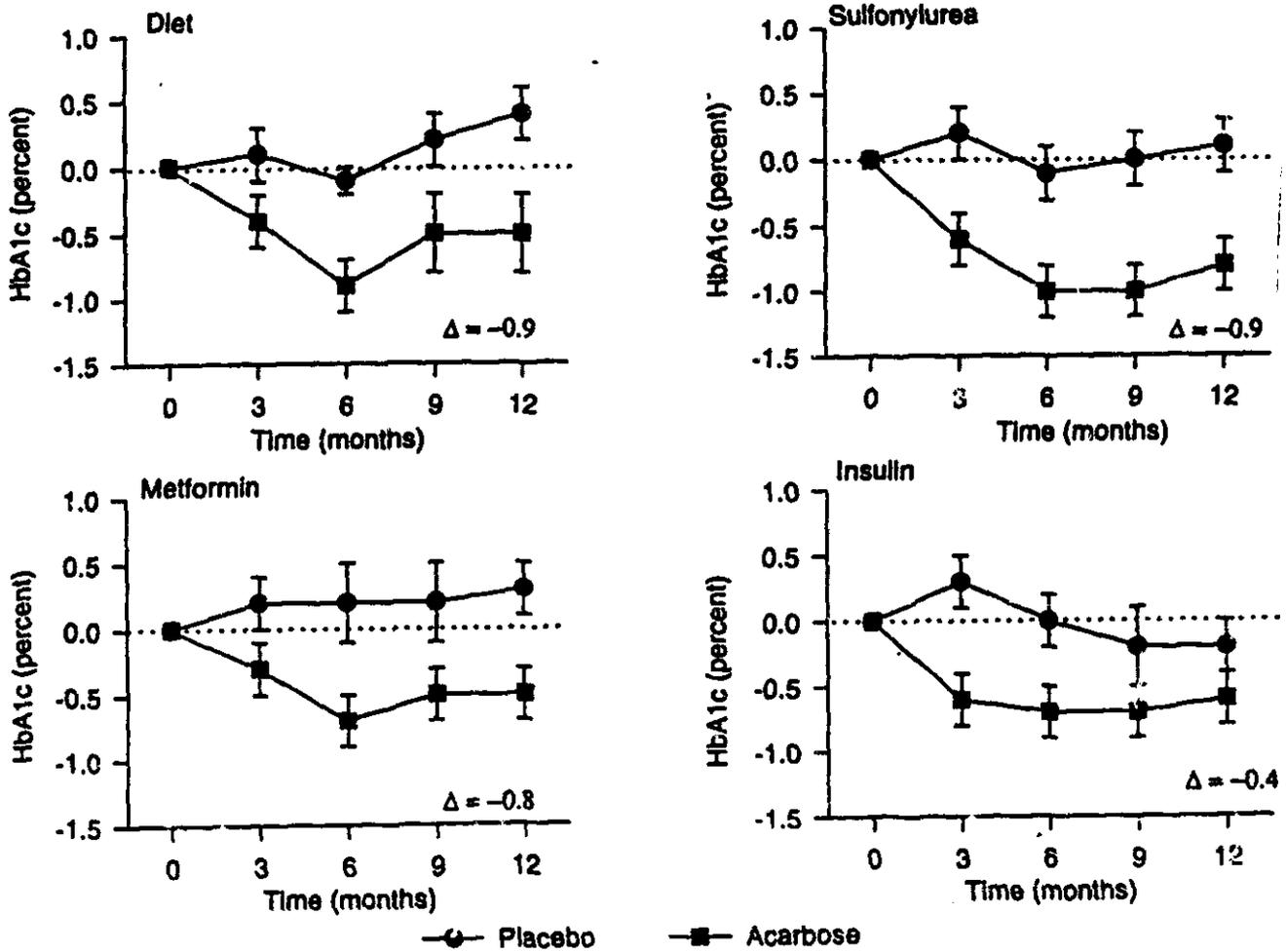


Figure 2

Mean Effect of Acarbose (25-300 mg tid) on HbA1c Levels

Population: Patients Valid for Efficacy

Acarbose + Diet Studies

- D86-006/052
- D86-008/054
- D91-006 - 100 mg tid
- 200 mg tid
- 300 mg tid

620

626

- 633 - 25 mg tid
- 50 mg tid
- 100 mg tid
- 200 mg tid

- 642 - 50 mg tid
- 100 mg tid

Acarbose + Sulfonylurea Studies

- D86-007/051
- D86-008/054
- 626

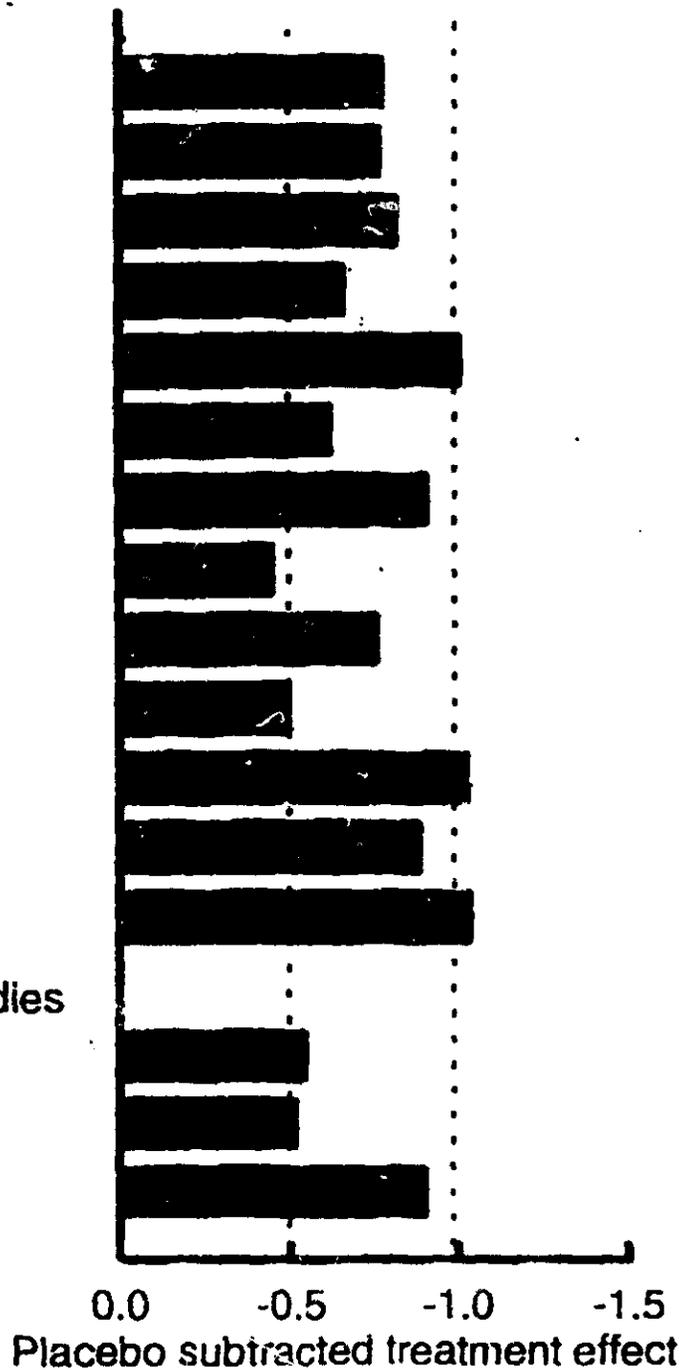
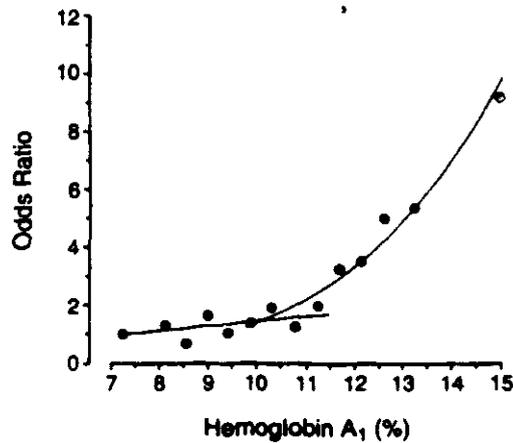


Figure 3

Krowlewski et al. N Engl J Med 332, 1353, 1995



Hemoglobin A _{1c} (%)	5.8	6.4	7.2	8.0	8.8	9.6	10.5	11.3	12.1
Blood glucose (mg/dl)	106	139	169	199	229	259	289	319	350

Figure 1. Relation between Mean Hemoglobin A_{1c} Values and the Risk of Microalbuminuria in Patients with IDDM.

Hemoglobin A_{1c} values were grouped into small intervals of equal width (0.45 percent, or 0.90 percent in the tails) and modeled with indicator variables in a logistic-regression model of the prevalence of microalbuminuria with covariates to adjust for the age at onset of diabetes, the duration of diabetes, and sex. The reference group for the adjusted relative odds (circles) was the group of patients with hemoglobin A_{1c} values ranging from 5.9 to 7.9 percent. A changepoint model, including the same covariates, was fitted to the logarithm of hemoglobin A_{1c} as a continuous variable to estimate the location of the changepoint and the regression slopes below and above the changepoint (continuous line). The horizontal axis shows hemoglobin A_{1c} values as well as the equivalent values of hemoglobin A_{1c} (see the Methods section) and the blood glucose profile.¹¹ In the DCCT, the blood glucose profile was determined by measuring the capillary-blood glucose concentration seven times in a 24-hour period (before and 90 minutes after each of the three major meals and before bedtime). The results of quarterly determinations of the blood glucose profile over a one-year period were averaged, and the line of regression was determined on the basis of the average of quarterly determinations of hemoglobin A_{1c} during the same year. To convert values for blood glucose to millimoles per liter, multiply by 0.05551.

Figure 4

Study 626
 Patient Characteristics by Stratum and Treatment Group

	Diet Alone (n = 77)		Diet & Insulin (n = 91)		Diet & Metformin (n = 83)		Diet & Sulfonylurea (n = 103)	
	Acarbose (n=38)	Placebo (n=39)	Acarbose (n=41)	Placebo (n=50)	Acarbose (n=41)	Placebo (n=42)	Acarbose (n=52)	Placebo (n=51)
Mean Age (years)	58	57	56	57	57	58	59	58
Sex (M/F)	22/16	26/13	24/17	28/22	25/16	28/14	31/21	27/24
Mean BMI (kg/m ²)	29	29	31	29	31	28	28	28
Mean Duration of Diabetes (years)	5.4	5.0	12.3	13	7.8	10	10	9
Race								
- Caucasian	36	37	39	45	39	38	47	45
- Others	2	2	2	5	2	5	5	6
Mean Baseline HbA1c (%)	6.7	6.6	7.7	7.8	7.8	7.8	8.1	8.0

The demographic data for all patients were comparable between treatment groups.

Table 1

All Adequate and Well-Controlled Studies
 Monotherapy and Combination Studies

POPULATION		TREATMENT EFFECT	
		WEIGHTED	UNWEIGHTED
All adequate and well-controlled studies	Patients valid for efficacy	-0.73	-0.76
	Intent to treat population	-0.73	-0.77
All adequate and well-controlled studies with the exception of the fixed dose groups of 25 mg tid from Study 633 and 300 mg tid from Study D91-006	Patients valid for efficacy	-0.74	-0.77
	Intent to treat population	-0.75	-0.77
All adequate and well-controlled studies with fixed doses of 50 mg tid, 100 mg tid or 200 mg tid	Patients valid for efficacy		
	all dose groups	-0.74	-0.77
	50 mg (n=131)	-0.77	-0.81
	100 mg (n=183)	-0.66	-0.78
	200 mg (n=290)	-0.78	-0.74
	Intent to treat population		
	all dose groups	-0.76	-0.78
	50 mg (n=145)	-0.78	-0.82
100 mg (n=211)	-0.72	-0.82	
200 mg (n=324)	-0.78	-0.73	

Table 2

JUL 13 1995

Acarbose
NDA 20,482

Safety update report submitted May 10, 1995

MEDICAL OFFICER'S REVIEW

1 The report makes reference to a 60 year old male who experienced an episode of acute encephalopathy associated with hypoglycemia while on acarbose. In response to a telephone inquiry for further details, I was informed by fax by M. Garvey on July 12th, 1995, that this patient had also been receiving insulin. Since the proposed package insert already warns that acarbose can potentiate the hypoglycemic effects of insulin, no additional action need be taken in light of this most recent report.

2 The spontaneous reports of adverse events have already been reviewed. Reference to spontaneous reports of cases of liver function abnormalities is already included in the package insert.

3 A discussion of the cohort of patients from study D90-025 who underwent sophisticated studies to examine the effect of acarbose on colonic environment has already been included in the medical review of the NDA. Attachment 2 provides some additional details, but it contains no new information that would require further action or comment.

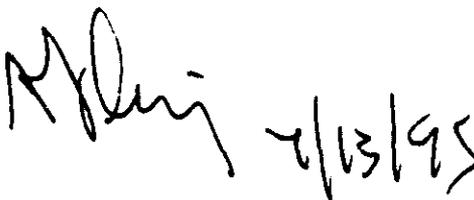
Summary:

The safety update of May 10, 1995 does not require that any action be taken.

Robert I Misbin MD
Medical Officer
July 12, 1995



HFD 510
NDA 20-482 Precose
HFD 510 A Fleming/J Short/ R Misbin



ORIGINAL

MAR 14 1995

STATISTICAL REVIEW AND EVALUATION

NDA#: 20-482

APPLICANT: Miles, Inc.

NAME OF DRUG: Precose (acarbose)

INDICATION: Non-Insulin-Dependent Diabetes Mellitus (Type II)

DOCUMENTS REVIEWED: Volumes 1.1-1.2, 1.137-1.143, 1.150 and 1.225 dated September 2, 1994 and submission dated January 17, 1995

MEDICAL REVIEWER: This review has been discussed with the clinical reviewers, Elizabeth Koller, M.D. and G. Alexander Fleming, M.D., HFD-510

RELEVANT ISSUES DISCUSSED IN THIS REVIEW

1. An HbA1c statistical treatment effect of acarbose in relationship to placebo has been demonstrated for a variety of fixed and titrated dosage regimens.
2. The clinical significance of the statistically positive HbA1c results needs to be determined based on the observed acarbose-placebo treatment effect which ranged from .4 to 1.0 across the sponsor's submitted studies.
3. Gastrointestinal adverse effects (e.g., flatulence) are statistically associated with acarbose.

Background

The sponsor has submitted NDA 20-482 dated September 2, 1994 in support of acarbose 50mg, 100mg, oral tablets as an adjunct to diet or diet plus sulfonylurea therapy in the treatment of patients with non-insulin-dependent diabetes mellitus (Type II, NIDDM) whose hyperglycemia cannot be satisfactorily controlled by diet alone.

Key Words: abdominal pain, clinical significance, diarrhea, diet, flatulence, gastrointestinal, glycosylated hemoglobin HbA1c, statistical significance, treatment effect.

Although studies have been conducted to evaluate the efficacy of acarbose in both NIDDM, the current application only seeks approval for the use of acarbose in NIDDM patients as an adjunct to diet or diet plus sulfonylurea therapy.

The sponsor has submitted the following "7 adequate and well-controlled studies" in support of the efficacy of acarbose as an adjunct to diet in NIDDM patients.

U. S. Studies

Non- U.S. Studies

D86-006/052	620
D86-008/054	626
D91-006	633
	642

The designs of studies D86-008/054 and 626 allow them to also be submitted in the support of the effectiveness of acarbose as an adjunct to diet plus sulfonylurea therapy. An additional U.S. Study, (Study D86-007/051) was also submitted to support the effectiveness of acarbose in combination with diet and sulfonylurea therapy.

Three (D86-006/052, D86-008/054, D86-007/051) of these 8 studies were resubmitted as they were included in the August 6, 1990 NDA submission. In fact, they were reviewed by this reviewer in a Statistical Review and Evaluation dated April 29, 1991. As indicated in the 1991 Statistical Review, the primary efficacy variable was the change from baseline in HbA1c, "which is thought to be the single most reliable indicator of overall glycemic control". In each of these studies, the acarbose patients experienced significantly greater reductions from baseline to endpoint (last double-blind observation) in HbA1c than did placebo patients. The HbA1c reductions (positive value indicates an increase) displayed below are taken from the designated tables of the 1991 Statistical Review:

<u>Study</u>	<u>Table</u>	<u>Acarbose</u>	<u>Placebo</u>	<u>P-value</u>
D86-006/052	3	-.06(-.08)	.53(.69)	.0001
D86-007/051	4	-.23(-.30)	.18(.24)	.02
D86-008/054	6	-.54(-.71)	.04(.05)	.001

The reductions displayed above were obtained by the Daiichi method which was employed in these studies. However, the

measurements obtained in the 5 remaining studies which are being submitted for the first time utilized the Diamat method. Results obtained by the Daiichi method were converted using the standard Affinity assay, to derive values (displayed in parenthesis above) corresponding exactly to those obtained by the Diamat method. The purpose of this conversion was to allow comparison of the HbA1c results obtained in the previously 3 submitted studies with those of the 5 newly submitted studies.

Despite the fact that statistical significance was achieved in favor of acarbose over placebo with respect to the reduction in HbA1c, it was concluded at the above mentioned July 25, 1991 advisory committee meeting that the acarbose HbA1c treatment effect was not clinically significant.

In reviewing the newly submitted above mentioned five studies (comments on each to follow), it is apparent that the results of these studies are consistent with the previously submitted 3 studies in that the clinical significance of these results is also in question in spite of the fact that statistical significance was once again achieved in favor of acarbose over placebo. These studies are also consistent with the previously submitted studies in that acarbose is statistically associated with gastrointestinal adverse events such as flatulence.

Study D91-006

This randomized, double-blind, multi-center (20 centers) U.S. placebo-controlled study was conducted "to compare the efficacy, tolerability, and safety of acarbose 100mg tid, 200mg tid, 300mg tid, and placebo, when employed in conjunction with diet, in the treatment of patients with type II diabetes mellitus."

Patients with a well established diagnosis of NIDDM for at least three months undergoing treatment with diet alone were eligible to participate. Eligible patients entered a two-week screening period which was followed by a four-week single-blind placebo run-in period and a 16-week double-blind treatment period. All patients were placed on a diabetic diet which was designed to maintain a stable body weight for the duration of the study.

The primary efficacy variable was "the change from baseline in glycosylated hemoglobin (HbA1c) after 16-weeks of double-blind therapy."

Reviewer's Comments on Study D91-006

A total of 290 (73 placebo, 73 acarbose 100mg tid, 72 acarbose 200mg tid, 72 acarbose 300mg) patients were randomized to receive double-blind treatment. Seventy-two (13 placebo, 20 acarbose 100mg, 18 acarbose 200mg, 21 acarbose 300mg, p = .39) patients prematurely discontinued study medication. The most common

discontinuation reason was the reporting of an adverse event (3 placebo, 12 acarbose 100mg, 15 acarbose 200mg, 14 acarbose 300mg, $p = .01$) with each of the acarbose treatment groups having a significantly ($p < .01$) greater percentage of patients withdrawing due to an adverse event than did the placebo treatment group.

As with regard to the clinical trials reviewed in the statistical review dated April 29, 1991, the most commonly reported adverse events were flatulence, diarrhea, and abdominal pain with flatulence and diarrhea achieving statistical significance (Table 1). However, there was no statistical indication of a dose response effect.

The results of the sponsor's intent-to-treat analyses of the change from baseline to the end of treatment in HbA1c is displayed in Table 2. In examining this table, one notes the existence of a highly significant ($p = .0001$) overall between-treatment group difference which is due to the fact that each of the acarbose treatment groups significantly ($p = .0001$) outperformed the placebo treatment group with respect to the mean reduction in HbA1c. However, as with regard to the above mentioned adverse event results, there was no statistical indication of a dose response effect.

One should note that the sponsor's proposed to be marketed dosage regimens of 100mg and 200mg yielded treatment effects (difference in change between acarbose and placebo) of .82 (-.41 versus .41) and .69 (-.28 versus .41) respectively. These treatment effects are similar to the corresponding Diamat treatment effects (.77 and .76) which were exhibited by the acarbose patients in the 2 previously submitted monotherapy studies D86-006/52 and D86-008/054 which were referred to in the background section of this review. Consequently, it appears that these results would also fail to satisfy the subjective clinically significant requirements established by the reviewing clinicians.

Study 626

This randomized, double-blind, multi-center (7 centers), Canadian, placebo-controlled study was conducted "to determine the long-term efficacy, tolerability and safety of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus."

Patients with a well documented primary diagnosis of NIDDM of at least six months duration undergoing therapy for at least one month with diet alone, diet and sulfonylurea, diet and biguanide (metformin), or diet and insulin were eligible to participate.

All patients entered a six-week pretreatment period in which they were placed on a diabetic diet which was designed to maintain a

stable body weight for the duration of the study. Subsequent to this six-week phase, patients were stratified according to their current hypoglycemic treatment (diet alone, diet and insulin, diet and metformin, diet and sulfonylurea) and then randomized to receive acarbose or placebo for 52 weeks of double-blind treatment.

Patients initially received 50mg tid of their randomized treatment. They were then titrated upward or downward to 100mg tid or 200mg tid over the first 24 weeks of the double-blind treatment phase based on tolerance, fasting glucose and post prandial 60 minute glucose levels following a standard test meal of Enrich, 450 Kcal.

The above mentioned dosage adjustments were not accompanied by increasing doses of sulfonylurea, metformin or insulin which were not permitted until after the 24 week double-blind treatment time point. Patients who had such sulfonylurea, metformin, or insulin dosage increases were included in the efficacy population only up to the point of time of such increase.

The primary efficacy criterion was the improvement of glycemic control based on the reduction in glycosylated hemoglobin levels (HbA1c).

Reviewer's Comments on Study 626

A total of 354 patients (Table 3) were randomized to receive double-blind treatment. Eighty-eight (46 acarbose, 42 placebo) patients prematurely discontinued study medication. The most common discontinuation reason was the reporting of an adverse event (33 acarbose, 20 placebo, $p = .03$), the most common of which was flatulence (15 acarbose, 4 placebo, $p = .01$).

As with regard to the previously mentioned clinical trials, the most commonly reported adverse events (Table 4) were flatulence, diarrhea, and abdominal cramps.

The results of the sponsor's HbA1c intent-to-treat analyses are displayed in Table 5. In examining this table, one should focus on the diet alone and diet plus sulfonylurea strata as the sponsor's submission (as discussed in the background section of this review) is in support of acarbose therapy as an adjunct to diet or diet plus sulfonylurea in the treatment of NIDDM. In doing so, one notes that acarbose patients significantly outperformed (diet alone: $p = .006$, diet plus sulfonylurea: $p = .001$) their placebo counterparts in each case. Once again, the acarbose monotherapy treatment effect (diet alone: .8), with regard to the reduction of HbA1c levels is consistent with those which were experienced by patients who were enrolled in the 2 previously submitted monotherapy studies which were referred to in the background section of this review, as well as with regard

to monotherapy Study 91-006. Consequently, it appears that the monotherapy results in this study would also fail to satisfy the subjective clinically significant requirements established by the reviewing clinicians.

However, the reviewing clinicians should note that the acarbose treatment effect (1.0) in the presence of sulfonylurea observed in this study is twice that exhibited in Study D86-007/051. The clinical significance of this finding needs to be addressed by the reviewing clinicians.

Study 620

This randomized, double-blind, single-center, West German study was conducted "to investigate the efficacy and tolerability of acarbose 100mg administered three times a day for 24 weeks to type II diabetics who were not adequately controlled by diet alone."

Subsequent to a four-week screening phase in which patients were on a diabetic diet alone, eligible patients were randomized to receive acarbose 100mg tid or matching placebo in addition to their diabetic diet for 24 weeks of double-blind treatment.

The primary efficacy variable was the change in HbA1 levels over the 24-week double-blind treatment period.

Reviewer's Comments on Study 620

A total of 100 (50 acarbose, 50 placebo) patients were randomized to receive double-blind treatment. Two patients (one in each treatment group) failed to complete the study. The acarbose patient withdrew due to gastrointestinal complaints, whereas the placebo patient withdrew due to the development of a foot ulcer.

A significantly ($p < .001$) greater proportion of acarbose patients (42/50) experienced at least one adverse event during double-blind treatment than did placebo patients (22/50). As with regard to previously mentioned studies, flatulence was the most commonly reported adverse reaction (acarbose: 39/50, placebo: 14/50, $p < .001$).

The patients were comparable at baseline across treatment groups with the exception of their duration of diabetes (acarbose: 76 months, placebo: 55 months, $p = .01$). However, there was no statistical evidence that the duration of diabetes influenced the HbA1 results.

The results of the sponsor's evaluable patient HbA1 analyses are displayed in Table 6. In examining this table, one notes that the acarbose patients experienced a significantly ($p = .003$) greater mean reduction in HbA1 than did placebo patients over the

double-blind treatment phase. In examining the HbA1 data for the 6 patients who were excluded from the sponsor's analyses, it was apparent to this reviewer that a similar result would have been obtained had these 6 patients been included in the analyses.

Consequently, the results of this study are consistent with those of the above mentioned studies in that a statistical treatment effect (in this case the acarbose-placebo HbA1 difference was .6) in favor of acarbose over placebo of marginal clinical importance was achieved in the presence of adverse gastrointestinal effects.

Study 623

This randomized, double-blind, multicenter (23 centers) European (Yugoslavia, Germany, Austria, Hungary, Italy) placebo-controlled study was conducted "to determine the efficacy of acarbose in improving glycemic control, i.e., glycosylated hemoglobin."

Patients with a well documented primary diagnosis of NIDDM for at least 6 months and no more than 5 years whom were being treated with diet alone were eligible to participate.

Subsequent to a six-week single-blind placebo phase, patients were randomized to receive placebo, acarbose 25mg, acarbose 50mg, acarbose 100mg, or acarbose 200mg administered tid for 24 weeks of double-blind treatment. Patients randomized to the acarbose 100mg and acarbose 200mg treatment groups commenced treatment on 50mg tid and 100mg tid respectively and continued their initial dosage for the first two weeks of the 24-week double-blind treatment phase.

The primary efficacy variable was the change from baseline in glycosylated hemoglobin HbA1c.

Reviewer's Comments on Study 623

A total of 636 (128 placebo, 127 acarbose 25mg, 127 acarbose 50mg, 128 acarbose 100mg, 126 acarbose 200mg) patients were randomized to receive double-blind treatment. Fifty-one (14 placebo, 10 acarbose 25mg, 6 acarbose 50mg, 14 acarbose 100mg, 7 acarbose 200mg) patients prematurely discontinued study medication. Fifteen (1 acarbose 25mg, 3 acarbose 50mg, 8 acarbose 100mg, 2 acarbose 200mg) of these discontinuations were due to gastrointestinal events (acarbose versus placebo: $p = .07$).

In examining the adverse event data submitted by the sponsor, I noted that once again flatulence (20 placebo, 47 acarbose 25mg, 60 acarbose 50mg, 60 acarbose 100mg, 75 acarbose 200mg) was the most commonly reported adverse event with its incidence being significantly ($p < .001$) greater in each of the acarbose treatment groups than in the corresponding placebo treatment group.

The results of the sponsor's HbA1c evaluable patient analyses (geometric means displayed as data was subjected to a logarithmic transformation due to the skewness of the distribution) are displayed in Table 7. In examining this table, one notes that each of the acarbose treatment groups statistically outperformed the corresponding placebo treatment group and that the acarbose-placebo treatment effects which ranged from .44 (acarbose 25mg) to 1.02 (acarbose 200mg) are in line with the treatment effects which were exhibited in the above mentioned studies. Similar results were obtained with respect to the intent-to-treat population.

Study 642

This randomized, double-blind, multi-center (2 centers) Italian placebo-controlled study was conducted to compare the efficacy and safety of acarbose and placebo in the treatment of NIDDM patients who have been treated with diet alone.

Patients with a well documented primary diagnosis of NIDDM were eligible to participate.

Subsequent to a 4-week single-blind placebo phase, patients were randomized to receive placebo, acarbose 50mg tid, or acarbose 100mg for 16 weeks of double-blind treatment. Patients were placed on a diabetic diet for the duration of the study in order to maintain a stable body weight.

The primary efficacy variable was the reduction from baseline in glycosylated hemoglobin (HbA1c).

Reviewer's Comments on Study 642

A total of 84 (29 placebo, 28 acarbose 50mg, 27 acarbose 100mg) patients were randomized to receive double-blind treatment. Thirteen (3 placebo, 6 acarbose 50mg, 4 acarbose 100mg) of these patients withdrew from the study. The most common withdrawal reason was the occurrence of an adverse event (1 placebo, 2 acarbose 50mg, 4 acarbose 100mg) five of which were gastrointestinal (1 placebo, 2 acarbose 50mg, 2 acarbose 100mg).

Once again, the most commonly reported adverse event was flatulence (7 placebo, 8 acarbose 50mg, 14 acarbose 100mg) as the acarbose 100mg incidence rate statistically ($p = .032$) exceeded the corresponding placebo rate.

The results of the sponsor's evaluable patient HbA1c analyses (similar results were obtained with regard to the intent-to-treat population) are displayed in Table 8. In examining this table, one notes that each acarbose treatment group experienced a significantly greater mean HbA1c reduction than did the corresponding placebo group and that the resulting treatment

effects (acarbose 50mg: .88, acarbose 100mg: 1.03 are consistent with those which were exhibited in the earlier mentioned studies.

Reviewer's Concluding Comments (may be conveyed to the sponsor)

The sponsor's September 2, 1994 submission reinforces the results presented in their August 6, 1990 NDA submission and discussed at a July 25, 1991 advisory committee meeting.

The main areas of reinforcement relate to the adverse gastrointestinal (especially flatulence) effects of acarbose as well as to the statistical demonstration of an HbA1c treatment effect.

It is apparent that treatment with acarbose in a variety of dosage forms (fixed or titrated) from 25mg tid to 300mg tid is statistically associated with a reduction in HbA1c levels. Consequently, the question that must be asked as it was at the July 25, 1991 advisory committee meeting is whether or not this statistically significant treatment effect can be also viewed as being a clinically significant treatment effect.

Table 9 which displays the treatment effects which were exhibited in the 8 studies which were included in the above mentioned two submissions, indicates that the HbA1c treatment effect is in the .4-1.0 range. Whether or not this can be viewed as being of any clinical importance is, of course, a matter of clinical judgement.

Daniel N. Marticello
Daniel N. Marticello
Mathematical Statistician

Concur: Dr. Nevius, *See 2-25-95*

Dr. Dubey *6 3-13-95*

CC:
Orig. NDA 20-482
HFD-510
HFD-510/Dr. Sobel
HFD-510/Dr. Koller
HFD-510/Dr. Fleming
HFD-510/Dr. Gueriguan
HFD-510/Mr. Short
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: DRU 1.3.2 NDA]
HFD-713/Group 2 File
HFD-713/Mr. Marticello
Chron.

Table 1
Study 91-006

Adverse Events*

Event	Placebo	Acarbose	Acarbose	Acarbose	P-value
		100mg	200mg	300mg	
Flatulence	17/73 (23.3%)	56/72 (77.8%)	62/71 (87.3%)	57/72 (79.2%)	<.001
Diarrhea	7/73 (9.6%)	24/73 (32.9%)	23/72 (31.9%)	26/72 (36.1%)	.001
Hypertension	0/73 (0.0%)	0/73 (0.0%)	4/72 (5.6%)	1/72 (1.4%)	.012
Headache	5/73 (6.8%)	11/73 (15.1%)	3/72 (4.2%)	13/72 (18.1%)	.022
Abdominal Pain	4/73 (5.5%)	13/73 (17.8%)	11/72 (15.3%)	14/72 (19.4%)	.075

* Adverse events for which the acarbose rate exceeds the placebo rate and p < .10

Table 2
Study 91-006

Sponsor's Intent-to-Treat HbA1c (%) Analyses

Pairwise Comparison⁺

	N	Baseline	Change⁺⁺	100mg	200mg	300mg
Placebo	71	8.90	.41	.0001	.0001	.0001
Acarbose 100mg	67	8.79	-.41		.45	.28
Acarbose 200mg	71	9.04	-.28			.06
Acarbose 300mg	69	9.48	-.59			
		p = .11	p = .0001			

⁺ Example: Acarbose 100mg versus Acarbose 200mg: p = .45

⁺⁺ Treatment by Center Interaction: p = .47

Table 3
Study 626

Randomized Patient Frequencies

Stratum	Acarbose	Placebo	Total
Diet Alone	38	39	77
Diet + Insulin	41	50	91
Diet + Metformin	41	42	83
Diet + Sulfonylurea	52	51	103
Total	172	182	354

Table 4
Study 626

Adverse Events

Flatulence

<u>Stratum</u>	<u>Acarbose</u>	<u>Placebo</u>
Diet Alone	28/38 (73.7%)	16/39 (41.0%)**
Diet + Insulin	33/41 (80.5%)	26/50 (52.0%)**
Diet + Metformin	28/41 (68.3%)	15/42 (35.7%)**
Diet + Sulfonylurea	37/52 (71.2%)	14/51 (27.5%)***

Diarrhea

<u>Stratum</u>	<u>Acarbose</u>	<u>Placebo</u>
Diet Alone	17/38 (44.7%)	5/39 (12.8%)**
Diet + Insulin	19/41 (46.3%)	11/50 (22.0%)*
Diet + Metformin	22/41 (53.7%)	13/42 (31.0%)*
Diet + Sulfonylurea	17/52 (32.7%)	8/51 (15.7%)*

Abdominal Cramps/Discomfort

<u>Stratum</u>	<u>Acarbose</u>	<u>Placebo</u>
Diet Alone	10/38 (26.3%)	5/39 (12.8%)
Diet + Insulin	11/41 (26.8%)	2/50 (4.0%)**
Diet + Metformin	7/41 (17.1%)	5/42 (11.9%)
Diet + Sulfonylurea	15/52 (28.8%)	4/51 (7.8%)**

* p < .05

** p < .01

***p < .001

Table 5
Study 626

Sponsor's Intent-to-Treat HbA1c (%) Analyses

Stratum	Acarbose			Placebo			P-value [†]
	N	Baseline	Change	N	Baseline	Change	
Diet Alone	32	6.6	-.4	39	5.6	.4	.006
Diet + Insulin	39	7.7	-.5	44	7.8	-.2	.097
Diet + Metformin	38	8.0	-.5	40	7.8	.3	.009
Diet + Sulfonylurea	51	8.2	-.9	47	8.0	.1	.001

[†] Acarbose versus placebo

Table 6
Study 620

Sponsor's Evaluable HbA1c (%) Endpoint Analyses

	Acarbose 100mg	Placebo
N	47	47
Baseline	9.30	9.40
Change	-.67*	-.06

* p = .003 in favor of acarbose over placebo

Table 7
Study 633

Sponsor's Evaluable HbA1c (%) Endpoint Analyses

	N	Baseline ++	Change++
Placebo	107	7.47	.31
Acarbose 25mg	110	7.45	-.13*
Acarbose 50mg	113	7.50	-.44*
Acarbose 100mg	103	7.47	-.18*
Acarbose 200mg	112	7.52	-.71*
			p = .001+

+ treatment by country interaction: p = .5
*p < .001 in favor of Acarbose over placebo
++ Geometric means

Table 8
Study 642

Sponsor's Evaluable HbA1c (%) Endpoint Analyses

	N	Baseline	Change
Placebo	23	7.23	.24
Acarbose 50mg	18	7.07	-.64*
Acarbose 100mg	23	7.15	-.79**
			p = .0001+

- * p < .001 in favor of Acarbose over placebo
- ** p < .0001 in favor of Acarbose over placebo
- + treatment by center interaction p = .61
Acarbose 50mg versus Acarbose 100mg: p = .57

Table 9

HbA1c+ Treatment Effects #

Study	Dosage (tid)	Treatment Effect
D86-006/052	50-300mg titrated	.77
D86-008/054	200mg	.76
D86-007/051	50-300mg titrated	.54
91-006	100mg	.82
	200mg	.69
	300mg	1.00
626	50-200mg titrated	.8-1.0
620	100mg	.61
633	25mg	.44
	50mg	.75
	100mg	.49
	200mg	1.02
642	50mg	.88
	100mg	1.03

+ HbA1 for Study 620

Acarbose reduction minus placebo reduction in HbA1c (Diamat method)

NDA 20-482
Precose® (50, 100, mg)
acarbose tablets

SUBMISSION DATE: July 19, 1995

Miles Inc., Pharmaceutical Div.
West Haven, CT 06516

REVIEWER: Hae-Young Ahn, Ph.D.

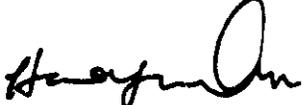
TYPE OF SUBMISSION: Response to a Bio-review Comment

Code: 1S

SYNOPSIS: The sponsor has submitted an amendment in response to the Comment of the Division of Biopharmaceutics' bio-review dated June 09, 1995. That Comment recommended the following dissolution method and specification for Precose tablets:

Apparatus Type:
Media:
Speed of Rotation:
Sampling Time:
Recommended Specification:

The Comment has been appropriately incorporated to their 7/19/95 NDA Amendment. Sampling times in the original NDA were 15 and 30 minutes. Now, a sampling time is replaced by 30 minutes. No further action is required.

 7/26/95

Hae-Young Ahn, Ph.D.
Reviewer, Division of Biopharmaceutics

RD initialed by J. Hunt
FT initialed by J. Hunt

7/26/95
 7/26/95

cc: NDA 20-482, HFD-510(Misbin and Short), HFD-340(Vish), HFD-426(Fleischer), HFD-427 (Ahn and M. Chen), Chron, Drug, Review, FOI(HFD-19)

JUL 18 1995

NDA 20-482
Precose® (50, 100, mg)
acarbose tablets

SUBMISSION DATE: June 09, 1995
June 27, 1995
July 06, 1995

Miles Inc., Pharmaceutical Div.
West Haven, CT 06516

REVIEWER: Hae-Young Ahn, Ph.D.

TYPE OF SUBMISSION: Amendments

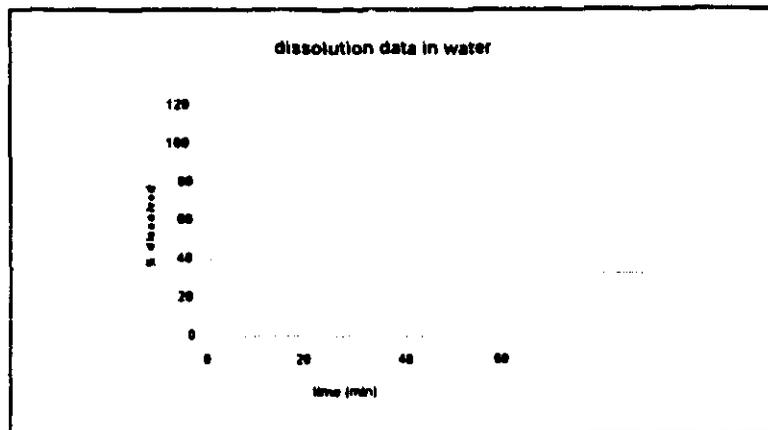
Code: 1S

SYNOPSIS: The sponsor has submitted three amendments to NDA 20-482 for Precose® (acarbose) which include a draft revised package insert, and additional dissolution data for i) the Precose® 50 mg tablet formulation that was used in pharmacokinetic studies and ii) half the to-be-marketed 50 mg tablet.

Lastly, the pharmacokinetic section of a draft package insert has been appropriately revised according to the Division of Biopharmaceutics' Labeling Comments.

Results:

It is concluded that the dissolution profiles of the to-be-marketed 50 mg formulation, the clinical trial 50 mg formulation and the PK study 50 mg formulation were essentially the same in water, simulated gastric fluid and simulated intestinal fluid. The plot of the dissolution profile of half tablets from the to-be-marketed 50 mg formulation in water shows a more rapid release of drug substance as compared with whole tablets. In all cases dissolution is nearly complete at the 30 minute time point and all batches meet the USP stage 1 limit ($Q = 75$ at 30 minutes) which was recommended by the Division of Biopharmaceutics in a bio-review stamp dated June 09, 1995.



RECOMMENDATION:

The Division of Biopharmaceutics has reviewed the amendment to NDA 20-482 for Precose® (acarbose) which was submitted on June 27, 1995. It has found that the draft revised package insert was acceptable. The Division of Biopharmaceutic has also reviewed two amendments which include additional dissolution data for the Precose® 50 mg tablet formulation used in pharmacokinetic studies and for half the to-be marketed 50 mg formulation. Two amendments that were submitted on June 09 and July 06, 1995 are also found to be acceptable.



Hae-Young Ahn, Ph.D.
Reviewer, Division of Biopharmaceutics

RD/FT initiated by J. Hunt



cc: NDA 20-482, HFD-510(Misbin and Short), HFD-340(Vish), HFD-426(Fleischer), HFD-427 (Ahn and M. Chen), Chron, Drug, Review, FOI(HFD-19)

JUN 9 1995

NDA 20-482
Precose™ (50, 100, mg)
acarbose tablets

SUBMISSION DATE: September 02, 1994
March 14, 1995 ·
March 22, 1995
April 10, 1995 ·
April 20, 1995 ·
April 21, 1995 ·
April 26, 1995 ·
May 12, 1995 ·
May 22, 1995 ·

Miles Inc., Pharmaceutical Div.
West Haven, CT 06516

REVIEWER: Hae-Young Ahn, Ph.D.

TYPE OF SUBMISSION: Original (NME)

Code: IS

SYNOPSIS:

The sponsor submitted a new NDA seeking approval for marketing acarbose 50 mg, 100 mg, and oral tablets which is indicated in the package insert as an adjunct to diet to lower blood glucose and glycated hemoglobin in patients with non-insulin-dependent diabetes mellitus whose hyperglycemia can not be satisfactorily controlled by diet alone. (Note: HbA_{1c} was used as an efficacy end point.) Acarbose is a competitive inhibitor of intestinal alpha-glucosidases. The proposed dosage range for acarbose is from 50 mg t.i.d. t where each dose is given with meals. However, several of the pharmacokinetic studies utilized a dosage of 300 mg t.i.d. in order to attain measurable plasma concentrations of drug. (Note: The 300 mg dose had once been considered as a maximum therapeutic dose.)

The original NDA was submitted in August, 1990 and it contained a ¹⁴C-bioavailability study, studies in the elderly and patients with renal impairment and liver impairment, drug-drug interaction studies with ranitidine and nifedipine, in vitro protein binding data, and a dissolution study. At that time the Division of Biopharmaceutics questioned the validity of the PK results due to the lack of assay specificity and assay validation data, and it recommended that more complete dissolution data be provided. The NDA was withdrawn in 1991 after an Agency's Advisory Committee meeting. Now, the sponsor has resubmitted an NDA with additional pilot PK studies and studies to address metabolism, dose-response relationships, PK in special populations and drug interactions. It is noted that the sponsor did not receive the biopharmaceutic comments from the original NDA submission's bio-review. Those comments have been restated in this review.

The assays used in the acarbose human pharmacokinetic studies were based on either the inhibition of alpha-glucosidases or nonselective radiometric measurement of ¹⁴C-acarbose. The former method detects the total activity of acarbose and active metabolites.

Through telephone conversations the following information was obtained from the sponsor:

1. All strengths were studied in the clinical trials and the acarbose tablets were taken with food.
2. For the 50 mg and 100 mg tablets, information on the batch/lot numbers were provided. The batches were not full scale production size batches but they represented at least 17 % of the number of dosage units for what full scale production size batches will be.
3. Two 100 mg tablets were used in the PK studies for a dose of 200 mg
However, in the clinical trials
4. Gender analyses were not conducted in the PK studies but they were conducted in the safety studies.
5. The sponsor submitted a reference article for concomitant administration of acarbose and a sulfonylurea drug (glibenclamide) in the PK section. They also conducted a few studies using combination sulfonylurea therapy in the clinical trials (*needs to be confirmed by the reviewing medical officer*).

The to-be-marketed 50 mg and 100 mg strength formulations were not tested in the pivotal clinical trials. Although the to-be-marketed formulations and the formulations used in the pivotal clinical trials have the same ratios of active and inactive ingredients, they are different in terms of the manufacturing of the drug substance and drug product. For the to-be-marketed formulations, drug substance was manufactured by a

while for the clinical trial formulations drug substance

drug substance For the PK study formulations employed for product

Comparative in vitro dissolution profiles were provided for the 50 mg tablets of the to-be-marketed formulation and the clinical trial formulation, 100 mg tablets of the to-be-marketed formulation, the clinical trial formulation and the PK formulation, clinically tested tablets upon request.

than the other strengths (50 and 100 mg) in the early time points, overall, dissolution profiles of all strengths (to-be-marketed formulations, clinical trial formulations and PK formulations) are similar in all three dissolution media (water, simulated gastric fluid and simulated intestinal fluid). Acarbose dissolution behavior is minimally affected by pH of the dissolution media.

RECOMMENDATION:

The Division of Biopharmaceutics (DB) has reviewed the biopharmaceutics section of NDA for Acarbose and has found it acceptable provided the Comments are addressed as appropriate. However, DB notes that the sponsor has conducted dissolution tests in water. Ideally, the sponsor should use a dissolution medium that is more physiologic condition (i.e., simulated gastric fluid). However, since the dissolution profiles of acarbose were essentially the same within the pH range of 1.2 to 7.8 and the sponsor conducted all its stability tests using water as a medium, DB recommends the dissolution test in water. Therefore, the following dissolution procedure and specification are recommended:

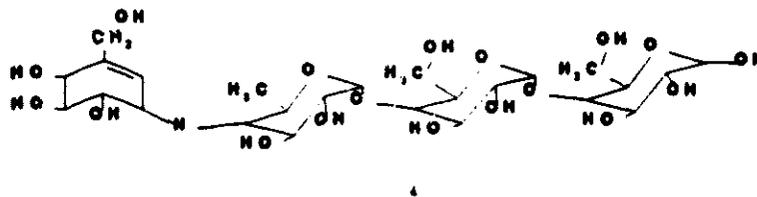
- Apparatus Type:
- Media:
- Speed of Rotation:
- Sampling Time:
- Recommended Specifications:

Please convey the Recommendation, the Comments and the Labeling Comments to the sponsor.

(Note: The Division of Biopharmaceutics is retaining the Appendices and Attachments within its drug files and can be obtained upon request.)

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BACKGROUND: Acarbose (BAY g 5421) is a pseudo-tetrasaccharide which inhibits the digestion of ingested carbohydrate, resulting in a smaller rise in blood glucose concentrations following meals.



NDA for acarbose was previously submitted on August 06, 1990 and the Division of Biopharmaceutics (DB) reviewed the biopharmaceutic section. The following information was quoted from the bio-review (stamp date of July 18, 1991) that was prepared by Dr. M. Daniel Gordin:

1. The pharmacologic action of acarbose occurs within the GI tract.
2. The systemic bioavailability of the parent compound is of no therapeutic relevance.
3. The demonstration of systemic availability of parent plus metabolite(s) following multiple dosing at the highest recommended dose (300 mg tid) to assess the extent of systemic exposure to acarbose plus metabolites is sufficient to characterize the product.
4. The validity of the results are questionable, since the enzyme assay was not sufficiently validated and the enzyme assay lacked specificity.
5. Additionally, comparative dissolution studies on the 50, 100, 200 and 300 mg tablets were requested.

Although a previous reviewer concluded that the systemic bioavailability of the parent compound is of no therapeutic relevance, safety concerns still remain and systemic exposure should be considered.

An Endocrinologic and Metabolic Drug Advisory Committee meeting was held on July 25, 1991 and the committee concluded that the acarbose data did not present a favorable benefit-to-risk relationship necessary for approval. The NDA was withdrawn by the sponsor on August 18, 1991.

There was a meeting held on 12/14/93 between the sponsor and HFD-510 to discuss the clinical data that was generated subsequent to the sponsor's withdrawal of NDA DB was invited to this meeting. The meeting was essentially a pre-NDA meeting for discussion of only clinical data. NDA 20-482 differs from the original NDA submission in the proposed indications, recommended dosing, and now it has additional dose-response and long-term safety data.

SUMMARY:

I. Bioavailability/Bioequivalency:

A. Bioavailability: After intravenous administration of 0.4 mg/kg acarbose, the plasma profile of acarbose plus active metabolite (component 2) was interpreted as a bi-phasic exponential function with a terminal half-life of 1.4 hr. Approximately 90% of the dose was found in the urine. After 300 mg of acarbose was given orally to volunteers, the mean C_{max} was 97 $\mu\text{g/L}$ at 2 hours. About 0.5% of the dose was recovered in the urine and 16.5% was excreted in faeces. (Note: The sponsor evaluated the pharmacokinetics of acarbose using an assay which could not distinguish acarbose and active metabolite.)

B. Bioequivalency:

A bioequivalence study was conducted using pharmacodynamic endpoints (plasma glucose and insulin levels). It was found that two tablet strengths (50 mg and 100 mg) were not bioequivalent in terms of PD endpoints using the Two One-side T-tests Procedure. The tablet formulations used in the bioequivalence study were, however, not the same formulations as those used in the clinical trials and the to-be-marked-formulation.

II. Metabolism:

After oral administration of ^{14}C acarbose to healthy volunteers, 35% of the radioactive dose was excreted in the urine in the form of at least 13 different biotransformation products. Three of these metabolites were isolated.

III. Dose-Response Relationship:

There was a dose-dependent increase in % inhibition of C_{max} for blood glucose levels although an ANOVA showed no significant difference between doses. There was a significant difference in % inhibition of AUC of blood glucose levels between the dose ($r=0.546$, $p<0.001$).

The ANOVAs showed significant differences in the % inhibition of C_{max} and AUC for blood insulin levels between doses ($p<0.01$, $p<0.001$, respectively).

IV. Protein Binding:

Less than 15% of acarbose is bound to plasma protein.

V. Pharmacokinetics in Special Populations:

A. Renal impairment: Patients with severe renal impairment ($\text{Cl}_{cr} < 25 \text{ ml/min/1.73m}^2$) attain about 5 times higher plasma peak concentrations of acarbose (plus an active metabolite) and 6 times larger AUC than volunteers with normal renal function.

B. Chronic liver disease: Pharmacokinetics of acarbose was not changed in patients with cirrhosis.

C. Elderly: After multiple dosing of acarbose for 7 days, AUC was increased about 30% and half life almost doubled (6.4 hr to 12.4 hr) in the elderly compared to normal volunteers.

VI. Drug-Drug Interactions:

- A. Nifedipine:** There was no interaction between acarbose and nifedipine.
- B. Ranitidine:** There was no significant interaction between acarbose and ranitidine.
- C. Cholestyramine:** Acarbose itself did not attenuate the post-prandial glycaemic response on any of the treatment days. It was concluded that the study design was not adequate to demonstrate any clinically significant interaction between acarbose and cholestyramine.
- D. Oral Contraceptive Pill:** It is unlikely that contraceptive efficacy will be lost when patients take a low-dose combination hormonal contraceptive agent with acarbose because a study showed that ovulation was still successfully suppressed with concomitant acarbose administration.
- E. Digoxin and Propranolol:** Acarbose did not affect the physiological effects or blood levels of digoxin or propranolol.
- F. Glibenclamide:** Student's t test showed that there were no significant differences in glibenclamide peak concentrations and AUC between the acarbose treated glibenclamide group and the placebo treated glibenclamide group. (Note: The study was from an article and raw data was not available.)

VII. PK/PD Analyses were not conducted.

VIII. Gender Analyses were not conducted in PK studies. However, it was learned that analyses were performed in safety studies.

VIV. Formulations:

The 50 and 100 mg formulations are proportionally similar in tablet ingredients except for the 50 and 100 mg formulation: used in the dose-ranging clinical study, 0633.
is

Table 1.

Strength (mg)	50	100
Formula Nos.	005 188-003 188-022	004 188-002 188-023
Ingredient	mg/tablet	
Acarbose	50	100
Dried Starch		
Microcrystalline Cellulose, NF		
Colloidal Silicon Dioxide, NF		
Magnesium Stearate, NF		
Total		

The *formula numbers* assigned to each tablet strength reflect differences in the manufacturing of the drug substance and/or drug product. Early batches were made with drug substance and tablet manufacturing was

Instead, they were produced

This information is summarized in Table 2.

Table 2

Strength	Formula No.	Drug Substance	Drug Product Granulation
50 mg			
100 mg			

Comments:

1. *The reviewing medical officer has indicated that the pivotal clinical trials used Formula Nos. 188-003 and 188-002 for 50 mg and 100 mg, respectively.*
2. *Formula Nos. 188-022 and 188-023 for 50 mg and 100 mg are the to-be-marketed formulations.*
3. *For the to-be-marketed formulations drug substance was manufactured by a _____; while for the clinical trial formulations drug substance was _____*
4. _____
5. *Human pharmacokinetic studies were conducted using Formula No. 005 and 004 for 50 mg and 100 mg, respectively.*

The formulations/formula numbers proposed for the marketed product are:

Table 4

Strength	Formula No.
50 mg	188-022
100 mg	188-023

In the dose-ranging clinical study 0633 different formulations were used. These formulations were designed specifically to facilitate blinding. The relative quantities of ingredients were adjusted to produce tablets of varying strengths but of identical size.

Table 3

Strength (mg)
Formula No.
Ingredient
Acarbose
Dried Starch
Microcrystalline Cellulose, NF
Colloidal Silicon Dioxide, NF
Magnesium Stearate, NF
Total

50	100
603	602
mg/tablet	
50	100

X. Dissolution:

The sponsor used the following dissolution method for acarbose tablets
 NLT after 30 minutes. However, the sponsor has claimed that at it has
 observed after the disintegration of a tablet, "accumulation of granulate" occurs in the bottom of the
 dissolution vessel instead of forming a complete suspension of granulates in the dissolution medium.
 As a result of this phenomenon, after 60 minutes,
 even though the active ingredient is extremely soluble in water. At 75 RPM, however, following
 free access to granulate particles allowing for better dissolution. Now the sponsor is proposing a
 dissolution method and specification as follows:

- (1) Dosage Form: Tablet
- (2) Strength(s):
- (3) Apparatus Type:
- (4) Media:
- (5) Speed of Rotation:
- (6) Sampling Time(s):
- (7) Proposed Specification: Minimum after 30 minutes.

The following were observed from the study:

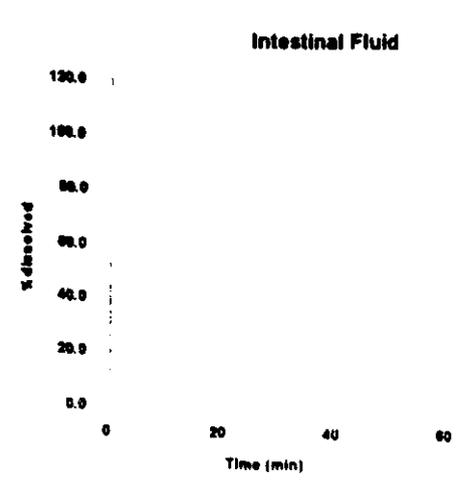
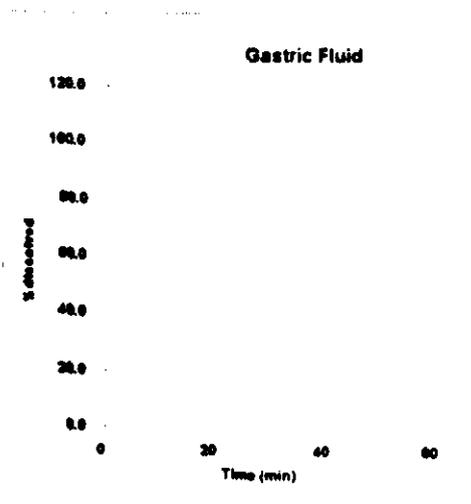
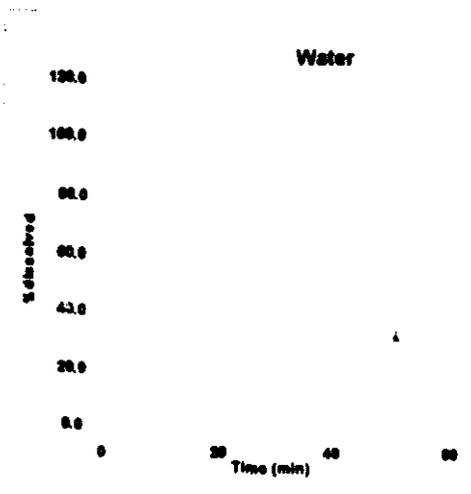
1. The 50 mg to-be-marketed formulation appears to have a faster dissolution profile than the 100 mg to-be-marketed formulations at 15 minutes (mean % dissolved in 15 minutes). Since of the drug was dissolved in 30 minutes, no differences were found.
2. The 100 mg to-be-marketed tablet formulation appears to have similar dissolution profiles as the 100 mg tablet formulation used in the PK studies and the 100 mg tablet formulation used in clinical trials at 15 minutes (mean % dissolved in 15 minutes).
- 3.
4. The dissolution information about the 50 mg tablets used in PK study at rpm was not provided.
5. On 03/31/95 the sponsor was requested to provide comparative in vitro dissolution studies on the 50, 100 mg tablets utilizing SGF without enzymes, SIF without enzymes and other media as appropriate using 12 dosage units per lot involving more than one dissolution sampling time point (5, 10, 15, 30, 60 minutes) for those lots used in the pivotal bioavailability and clinical studies. In addition, pH solubility profiles was also requested for acarbose. (Note: In Dr. Gordin's previous bio-review this same information was requested to be provided by the sponsor.)

The sponsor had conducted dissolution tests upon official request from HFD-510 and submitted the following:

Dosage (mg)	Formulation Number	Batch Number	Date of Manufacture	Expiration Status
50	188-022	CL-15-47	June 2, 1993	not expired
50	188-003	FA-9-61	June 23, 1987	expired
100	188-002	FA-9-66	June 24, 1987	expired
100	188-023	SP-01-53	April 30, 1990	expired
100	004	531253A	August 10, 1994	not expired

Dissolution Condition: USP apparatus and simulated intestinal fluid at rpm.

of water, simulated gastric fluid



Age of tablets does not seem to affect the dissolution behavior of acarbose. Acarbose dissolution behavior is minimally affected by pH of the dissolution media, although dissolution in simulated gastric fluid appears to be more rapid as compared with other media for each dose. The sponsor concluded that the dissolution profiles of the formulations tested were essentially the same within the pH range of 1.2 to 7.8. This reviewer, however, noted that the tablets appear to have a somewhat slower dissolution profile than other strengths (50 and 100 mg) in early time points in all three dissolution media.

GENERAL COMMENTS:

1. A study in which a tablet and an oral solution (or iv solution) were administered in a crossover design in order to determine systemic bioavailability was not conducted; however, the sponsor combined the results of two separate studies in which subjects were administered a 0.4 mg/kg iv dose in one and a single oral 300 mg tablet dose in the other. The absolute acarbose bioavailability was determined to be 1.5%.

2. For Study No. 510 approximately 86.7% of the administered radio-labelled dose was accounted for over 96 hrs by urine and fecal collection. This was broken down as approximately 35.4% of the radioactivity was recovered in the urine and approximately 51.3% was recovered in the faeces which can include both biliary elimination and unabsorbed drug from the GI tract. The 35.4% of radioactivity recovered in the urine consisted of 1.7% parent acarbose and the remainder as metabolite(s). [It is not clear to this reviewer how the sponsor determined these values since the enzyme assay is not specific.] The sponsor contends that this gives an indication that less than 2% acarbose and > 30% of its metabolites are absorbed (i.e. bioavailable) following an oral dose. However, this does not take into account drug which may be absorbed and then is fecally eliminated via the biliary route. So these values may underestimate the systemic bioavailability of acarbose and its metabolites.

Not sent to Bay

LABELING COMMENTS:

Pharmacokinetic section in Clinical Pharmacology is recommended to change as follows:

Absorption

Revised in 6/21/95 submission
Less than 2% of an oral dose of acarbose is absorbed as active drug, while approximately 35% of total radioactivity from a ¹⁴C-labeled oral dose is absorbed. An average of 51% of an oral dose is excreted in the feces as unabsorbed drug-related radioactivity within 96 hours of ingestion. Since acarbose acts locally within the gastrointestinal tract, this low systemic bioavailability of parent compound is therapeutically desired. Following oral dosing of healthy volunteers with ¹⁴C-labeled acarbose, peak plasma concentrations of radioactivity were attained 14-24 hours after dosing, while peak plasma concentrations of active drug were attained at approximately 1 hour. The delayed absorption of acarbose-related radioactivity reflects the absorption of metabolites which may be formed by either intestinal bacteria or enzymatic hydrolysis. Plasma concentrations of acarbose-related radioactivity were 10-20 times greater than the corresponding concentrations of active drug.

Metabolism

Acarbose is metabolized exclusively within the gastrointestinal tract, principally by intestinal bacteria, but also by digestive enzymes. A fraction of these metabolites (approximately 34% of the dose) is absorbed and subsequently excreted in the urine. At least 13 metabolites have been separated chromatographically from urine specimens. The major metabolites have been identified as 4-methylpyrogallol derivatives (i.e., sulfate, methyl and glucuronide conjugates). One metabolite (formed by cleavage of a glucose molecule from acarbose) also has alpha-glucosidase inhibitory activity which, however, is less than that of the parent compound(needs to be deleted). This metabolite, together with the parent compound, accounts for less than 2% of the total administered dose. The metabolic pathway of acarbose in man is similar to that in rats .

Excretion

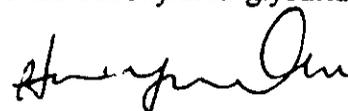
The fraction of acarbose that is absorbed as intact drug is almost completely excreted by the kidneys. When acarbose was given *intravenously*, 89% of the dose was recovered in the urine as active drug within 48 hours. In contrast, less than 2% of an *oral dose* was recovered in the urine as active drug. This is consistent with the low bioavailability of the parent drug. The plasma elimination half-life of acarbose activity is approximately 2 hours in healthy volunteers. Consequently, substantial accumulation does not occur with three times a day (t.i.d.) oral dosing.

Special Population

Plasma concentrations of acarbose in elderly volunteers were not significantly higher than those observed in young volunteers. However, the mean steady state area under the curve and maximum concentration of acarbose were approximately 1.5 times higher in the elderly compared to the young(needs to be added). Patients with severe renal impairment (Clcr <25 ml/min/1.73m²) attain about 5 times higher plasma peak concentrations of acarbose (plus an active metabolite) and 6 times larger AUC than volunteers with normal renal function.

Drug-Drug Interaction

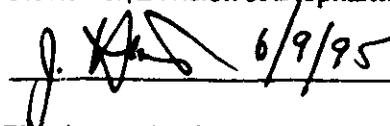
Studies in healthy volunteers have shown that PRECOSE has no effect on either the pharmacokinetics or pharmacodynamics of digoxin, nifedipine, propranolol, or ranitidine. PRECOSE did not interfere with the absorption or disposition of the sulfonylurea glyburide in diabetic patients.

 6/09/95

Hae-Young Ahn, Ph.D.

Reviewer, Division of Biopharmaceutics

RD/FT initiated by J. Hunt

 6/9/95

Biopharm Day (6/08/95, Ludden, Malinowski, Chen, Hunt, Fleming and Misbin)

cc: NDA 20-482, HFD-510(Misbin and Short), HFD-340(Vish), HFD-426(Fleischer), HFD-427 (Ahn and M. Chen), Chron, Drug, Review, FOI(HFD-19), Food, E, R, H

FEB - 3 1995

NDA 20-482

Feb. 3, 1995

Miles Inc.
West Haven, CT

Submission date: Sept. 2, 1994

ORIGINAL

Pharmacology Review of NDA

Drug: Precose; acarbose

Category: Hypoglycemic Agent

Related: Previous submission of

*2 labeling
comments
conveyed in
letter dated
5/30/95
and
replied
in 6/27/95
Autman*

This review summarizes submissions since the last NDA.

Bay o 1248/Altromin C1009 - Studies in female sprague-Dawley rats on the subject of carcinogenic action in the kidneys as a result of reduced glucose utilization. Report No. PH 23021, 1994.

Groups of 70 female Sprague-Dawley rats were given in the feed Bay o 1248 (emiglitate) at 5000 ppm with a std diet, a low carbohydrate diet (from wk 60 supplemented with 10% std diet), or std diet alone for 137 wks.

The low carbohydrate diet led to severe growth retardation, higher feed consumption, and increased mortality. Emiglitate administration resulted in growth retardation, slightly increased feed consumption, and an increase in kidney tumors.

Emiglitate is an alpha glucosidase inhibitor (similar to acarbose) but with a different chemical structure, metabolism and excretion. The fact that it produced kidney tumors in Sprague-Dawley rats is evidence that the kidney carcinogenic potential of acarbose is due to its mode of action and not inherent in any direct action of acarbose or its metabolites or its excretion pattern.

Also, emiglitate did not produce kidney tumors in Wistar rats (similar to acarbose).

Tumor type	controls	emiglitate
No. animals	50	50
Adenoma	4	11
Adenocarcinoma	0	6
Histiocytic sarcoma	1	0
Giant-cell sarcoma	0	1

It is believed that the glucose deprivation of the degree seen in the rat studies will not occur in people taking the drug.

Embryotoxicity study on rats after oral administration (rearing part). Report No. 18173 (E), 1989.

Pregnant BAY:FB 30 rats (15/gp) were given acarbose orally at doses of 0 or 480 mg/kg body wt. from days 6-15 of pregnancy. The dams did not undergo caesarian section but were allowed to litter and rear their pups.

Maternal body wt or any indices of pregnancy (except prenatal loss, which was not seen in an earlier study) were not affected by drug treatment. The parameters of perinatal and postnatal development (course of labor, postnatal mortality and physiological development of the offspring) were similar to controls.

At least one male and one female from each litter were raised to maturity and mated. Treatment of the dams did not have any adverse effects on the fertility of the F₁ generation.

Evaluation of the systemic exposure to acarbose and its radioactive metabolites in male Sprague-Dawley rats dosed via food or gavage and in male Wistar rats dosed via food. Report No. 21915 (P), 1992.

Following pretreatment with cold acarbose for 14 days, [¹⁴C]Acarbose was administered to male Sprague-Dawley and Wistar rats with food at doses of 150, 1500, and 4500 ppm and to male Sprague-Dawley rats by gavage (12, 120, 360 mg/kg b.w.) in a single oral dose. The systemic exposure to acarbose and its metabolites increased with dose in all gps. The metabolic patterns were qualitatively comparable between doses, rat strains, and modes of administration. No relevant quantitative differences in the systemic exposure were found between rat strains and, at least for the high dose gps, for the different routes of administration.

Evaluation of the systemic exposure to acarbose and its radioactive metabolites in male Sprague-Dawley rats dosed via diet with and without glucose supplementation. Report No. 23007, 1994.

Following a pretreatment with cold acarbose in diet either with or without glucose (30% by wt) for 14 days, [¹⁴C]acarbose was administered to male Sprague-Dawley rats with the two diets (4500 ppm) orally for 24 hrs. No quantitative differences in the pharmacokinetics of acarbose and its radioactive metabolites were found between the two gps. The metabolic patterns were qualitatively similar. Thus, there was no evidence for an alteration of the systemic exposure to acarbose and its metabolites due to glucose supplementation in rats.

Conclusion: The new data provide evidence that the carcinogenicity of acarbose is probably due to glucose deprivation and seems to be restricted to Sprague-Dawley rats. A

similar glucosidase inhibitor, emiglitate, which has a different structure from acarbose, also produced tumors in Sprague-Dawley but not Wistar rats. Because the chemical structures, metabolites, and elimination patterns are different between the two drugs, the results suggest that the carcinogenicity of acarbose is due to the glucose deprivation in a sensitive strain of rat.

COMMENTS TO SPONSOR

Labelling: Under Precautions; Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Paragraph 47; Replace the second sentence with "Acarbose treatment resulted in a significant increase in the incidence of renal tumors (adenomas and adenocarcinomas) and benign Leydig cell tumors."

Paragraph 51; Delete.

Paragraph 52; Delete the second sentence and the last sentence.

Under Pregnancy: Teratogenic Effects: The dose multiple of 54948 seems to be based on mg/kg doses instead of on drug blood levels. The high dose was 480 mg/kg in the teratology studies and the highest recommended dose in patients is approximately 10 mg/kg. Based on the AUC's of total radioactivity given in the acarbose ADME Technical Summary in Vol. 8, a multiple of 9 would seem more appropriate.

~~Paragraph 54; Delete.~~ AJ 5/11/95

Recommendation: Pharmacology recommends approval of acarbose for the control of blood glucose.

AJ Jordan

Alex Jordan, PhD

NDA 20-482
HFD-510

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510

Review of Chemistry, Manufacturing and Controls

NDA #: 20-482

CHEMISTRY REVIEW #: 3

DATE REVIEWED: 7-26-95

JUL 26 1995

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9-6-94	9-8-94	9-8-94
AMENDMENT	6-19-95	6-20-95	
	6-27-95		
	7-5-95	7-6-95	
	7-6-95	7-7-95	

NAME & ADDRESS OF APPLICANT:

Bayer Corporation.
400 Morgan Ln
West Haven, CT 06516-4175
203-937-2000

DRUG PRODUCT NAME

Proprietary: Precose
Nonproprietary/Established/USAN: Acarbose tablets
Code Name/#: Bay g 5421
Chem. Type/Ther. Class: 1 S

PHARMACOLOGICAL CATEGORY/INDICATION: Hypoglycemic agent/Type II Diabetes

DOSE FORM: Tablet

STRENGTHS: 50mg, 100mg

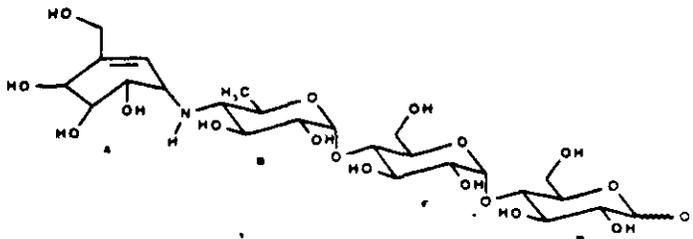
ROUTE OF ADMINISTRATION: Oral

DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

$C_{25}H_{45}NO_{18}$
MW = 645.62

O-4,6-dideoxy-4-
[[1S,4R,5S,6S)-4,5,6-
trihydroxy-3-(hydroxymethyl)-
2-cyclohexen-1-yl]amino]- α -D-
glucopyranosyl-(1 \rightarrow 4)-O- α -D-
glucopyranosyl-(1 \rightarrow 4)-D-
glucose



CONCLUSIONS & RECOMMENDATIONS:

This NDA is approvable from chemistry point of view. FUR was cleared on 7-24-95 and the comparable dissolution data was found to be satisfactory by Biopharm (7-18-95). The only pending chemistry issue is satisfactory review of EA (consult was sent on 7-10-95).

Org. NDA 20-482
HFD-510/Division File
HFD-510/MRhee/YChiu/JShort

R/D Init by: SUPERVISOR
filename: NL-1. 205

YChiu
7/26/95

Moo-Jhong Rhee

Moo-Jhong Rhee, Ph.D.
Review Chemist

consult completed 8/8/95

FAR to firm 8/9/95

Amendment from firm dated 8/10/95

hand carried copy

JUL 25 1995

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA #: 20-482

CHEMISTRY REVIEW #: 2

DATE REVIEWED: 7-25-95

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	9-6-94	9-8-94	9-8-94
AMENDMENT	6-19-95	6-20-95	
	6-27-95		
	7-5-95	7-6-95	
	7-6-95	7-7-95	

NAME & ADDRESS OF APPLICANT:

Bayer Corporation.
400 Morgan Ln
West Haven, CT 06516-4175
203-937-2000



DRUG PRODUCT NAME

<u>Proprietary:</u>	Precose
<u>Nonproprietary/Established/USAN:</u>	Acarbose tablets
<u>Code Name/#:</u>	Bay g 5421
<u>Chem.Type/Ther.Class:</u>	1 S

PHARMACOLOGICAL CATEGORY/INDICATION: Hypoglycemic agent/Type II Diabetes

DOSAGE FORM: Tablet

STRENGTHS: 50mg, 100mg

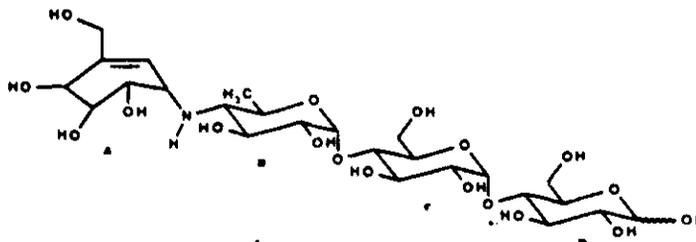
ROUTE OF ADMINISTRATION: Oral

DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

$C_{25}H_{43}NO_{18}$
MW = 645.62

O-4,6-dideoxy-4-
[[1S,4R,5S,6S)-4,5,6-
trihydroxy-3-(hydroxymethyl)-
2-cyclohexen-1-yl]amino]- α -D-
glucopyranosyl-(1 \rightarrow 4)-O- α -D-
glucopyranosyl-(1 \rightarrow 4)-D-
glucose



CONCLUSIONS & RECOMMENDATIONS:

This NDA is approvable pending satisfactory FUR (forwarded 6-28-95) and satisfactory reviews of the response to EA's previous deficiencies (consult was sent on 7-10-95) and comparative dissolution data of the 50mg scored tablets by Biopharm (consult was sent on 7-10-95). Summary of Chemistry Review is attached.

cc:

Org. NDA 20-482

HFD-510/Division File

HFD-510/MRhee/YChiu/JShort

R/D Init by: SUPERVISOR

filename: NL-1. 205

YChiu
7/25/95

completed and OK.

Moo-Jhong Rhee, Ph.D.
Review Chemist

REMARKS/COMMENTS:

The 6-19-95 amendment was submitted in response to the deficiencies conveyed to the sponsor through fax on 5-24-95.

The 6-27-95 amendment has revised package insert,

The 7-5-95 submission is the firm's response to the deficiencies observed in EA and sent for consult on 7-10-95

The 7-6-95 amendment contains a revised specification for the new scored 50mg tablets, and dissolution data of 25mg (half of 50mg tablet) and scored 50mg tablets for Biopharm review (consult was sent on 7-10-95). Also contained is revised specification for "Appearance" to read "Precose 50 (with score on the back)" and "precose 100", respectively.

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA #: 20-482

CHEMISTRY REVIEW #: 1

DATE REVIEWED: 5-18-95

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE

ORIGINAL	9-6-94	9-8-94	9-8-94
AMENDMENT	3-13-95		
	4-10-95		

*Comments
fax'd 5/24/95
and response
dated 6/19/95*

NAME & ADDRESS OF APPLICANT: Bayer Corporation.
400 Morgan Ln
West Haven, CT 06516-4175
203-937-2000

DRUG PRODUCT NAME

Proprietary:	Precose
Nonproprietary/Established/USAN:	Acarbose tablets
Code Name/#:	Bay g 5421
Chem. Type/Ther. Class:	1 S

ANDA Suitability Petition / DESI / Patent Status: N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION: Hypoglycemic agent/Type II Diabetes

DOSAGE FORM: Tablet

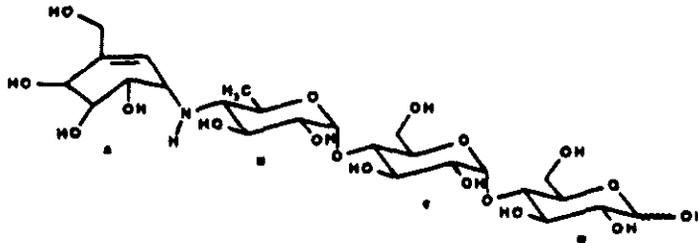
STRENGTHS: 50mg, 100mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: Rx OTC

CHEMICAL NAME. STRUCTURAL FORMULA. MOLECULAR FORMULA. MOLECULAR WEIGHT:

$C_{28}H_{43}NO_{18}$
MW = 645.62



O-4,6-dideoxy-4-
[[1S,4R,5S,6S]-4,5,6-
trihydroxy-3-(hydroxymethyl)-
2-cyclohexen-1-yl]amino]- α -D-
glucopyranosyl-(1 \rightarrow 4)-O- α -D-glucopyranosyl-(1 \rightarrow 4)-D-glucose

CONCLUSIONS & RECOMMENDATIONS:

This NDA is approvable pending satisfactory resolution of deficiencies delineated in the draft letter and EA review. EER was returned with acceptable rating (3-29-95).

cc:
Org. NDA 20-482
HFD-510/Division File
HFD-510/MRhee/YChiu/JShort

R/D Init by: SUPERVISOR
filename: NL. 205

*YChiu
5/19/95*

Moo-Jhong Rhee, Ph.D.
Review Chemist

SUPPORTING DOCUMENTS:

Related Document:

REMARKS/COMMENTS:

Originally, this NDA was submitted on 8-6-90 as NDA _____ and Chem Review #1 was completed on 2-12-91 with 'approveable' recommendation. Information request letter was issued on 2-28-91. However, on 8-6-91, the NDA was withdrawn. Before the NDA was withdrawn, the firm responded to the deficiencies on 4-16-91.

On 9-6-94, the firm resubmitted a new NDA 20-482, which is essentially the same as the withdrawn NDA _____ with the previous deficiencies addressed. On 3-13-95, at the request through a telephone conversation (3-10-95), the firm incorporated the DMF _____ into this new NDA 20-482 as a drug substance section and stated in 4-10-95 amendment that this NDA is no longer cross-referencing to the DMF . Previously, this DMF also had deficiencies and the DMF holder responded to the deficiencies in their 5-6-91 amendment to the DMF

Since this new NDA 20-482 is a combination of the DMF _____ and previously withdrawn NDA _____ chemistry review was rewritten with previous questions or information request (including DMF's) recited in each relevant section of this review.

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT

PRECOSE™

(acarbose tablets)

50 and 100 mg

NDA 20-482

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF METABOLISM and ENDOCRINE
DRUG PRODUCTS (HFD-510)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-482

PRECOSE

(acarbose tablets)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for PRECOSE Tablets, Bayer Corporation has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Acarbose is a naturally occurring pseudotetrasaccharide produced by microorganisms of the genus *Actinoplanes* and is administered as an oral tablet in the treatment of non-insulin dependent diabetes mellitus (Type II). The drug substance will be manufactured by Bayer AG, Germany and the drug product will be manufactured and packaged by Bayer, West Haven, CT. The finished drug product could be used in hospitals, clinics and by patients in their homes.

Acarbose may enter the environment from excretion by patients, as emissions from manufacturing sites or from disposal of pharmaceutical wastes. Chemical and physical test results indicate that the majority of the drug substance will most likely be restricted to the aquatic environment. Data indicate that the material is susceptible to biodegradation.

As acarbose would be expected to persist in the aquatic environment for some time, the toxicity of the material to organisms was characterized. Acute static toxicity studies in water fleas (*Daphnia magna*), fish (*Brachydanio rerio*) and testing of bacteria (*Pseudomonas putida*) indicate that the drug substance is not toxic to organisms at the expected environmental concentrations.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Waste drug substance and drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

8/17/95 Nancy B Sager
DATE PREPARED BY
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

8/17/95 R. A. Jerussi
DATE CONCURRED
Robert A. Jerussi, Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Material Safety Data Sheet
Certificate of Compliance, Germany
Certificate of Compliance, West Haven, CT

**Precose™ (acarbose tablets) 50 mg and 100 mg
Bayer Corporation, Pharmaceutical Division - West Haven CT**

**NDA SECTION 3A
CHEMISTRY, MANUFACTURING, AND CONTROLS**

ENVIRONMENTAL ASSESSMENT

**Bayer AG
Wuppertal-Elberfeld, Germany**

**Bayer Corporation
Pharmaceutical Division
West Haven CT**

Precose™ (acarbose tablets) 50 mg and 100 mg
Bayer Corporation, Pharmaceutical Division - West Haven CT

ENVIRONMENTAL ASSESSMENT

Table of Contents

1.	Date	03-03A-0000003
2.	Name of Applicant	03-03A-0000003
3.	Address	03-03A-0000003
4.	Description of the Proposed Action	03-03A-0000003
5.	Identification of the Chemical Substance	03-03A-0000005
6.	Introduction of Substances into the Environment	03-03A-0000006
7.	Fate of Emitted Substances in the Environment	03-03A-0000008
8.	Environmental Effects of Released Substances	03-03A-0000008
9.	Use of Resources and Energy	03-03A-0000009
10.	Mitigating Measures	03-03A-0000009
11.	Alternatives to the Proposed Action	03-03A-0000009
12.	List of Preparers	03-03A-0000009
13.	Certification	03-03A-0000010
14.	References	
	a. Merck Index, 11th ed.	03-03A-0000011
15.	Appendices	
	a. Acarbose Material Safety Data Sheet (MSDS)	03-03A-0000013
	b. Physical and Chemical Properties of Acarbose	03-03A-0000018
	c. Acarbose Absorption Spectrum	03-03A-0000020
	d. Structures of Major Metabolites of Acarbose	03-03A-0000023
	e. Chemical and Biological Degradation of Acarbose	03-03A-0000026
	f. Environmental Effects of Acarbose	03-03A-0000028
	g. Study Report 254 A/91: Ecological Properties of Acarbose	03-03A-0000030
	h. MEEC for the Aquatic Compartment	03-03A-0000065
	i. Federal Requirements (Germany)	03-03A-0000067
	j. Certificate of Compliance - Düsseldorf, Germany	03-03A-0000069
	k. Regulatory Overview (West Haven CT)	03-03A-0000075
	l. Certificate of Compliance - Bayer, West Haven CT	03-03A-0000077
	m. Description of Clean Harbors Inc. Facility	03-03A-0000079
	n. Curricula Vitae of the Preparers	03-03A-0000081

**Precose™ (acarbose tablets) 50 mg and 100 mg
Bayer Corporation, Pharmaceutical Division - West Haven, CT**

Environmental Assessment

1. **Date:**

July 5, 1995

2. - **Name of Applicant/Petitioner:**

Bayer Corporation
Pharmaceutical Division

3. **Address of Applicant/Petitioner:**

400 Morgan Lane
West Haven CT 06516

4. **Description of the Proposed Action:**

a) **Description of the Requested Approval**

The proposed action is manufacturing and packaging of Bayer Corporation, Pharmaceutical Division's drug product Precose™ (acarbose tablets) 50 mg and 100 mg under New Drug Application (NDA) 20-482.

b) **Need for the Action**

Approval of the NDA will make Precose® available as an adjunct to diet to lower blood glucose and glycated hemoglobin in patients with non-insulin-dependent diabetes mellitus (Type II) whose hyperglycemia cannot be satisfactorily controlled by diet alone.

c) **Locations Where the Product Will Be Produced**

i. **Bayer AG, Germany** - The drug substance will be produced at Bayer AG's Wuppertal-Elberfeld facilities in

Buildings 150b, 152a, 152b, and 153
Freidrich Ebert Strasse, 217-399
D-42096 Wuppertal, Germany

The facilities are located in an urban environment. The surrounding area is hilly with a temperate climate.

ii. **Bayer, West Haven CT** - The drug product will be manufactured and packaged at Bayer Corporation's Pharmaceutical Division facilities in

Building A21
400 Morgan Lane
West Haven, CT 06516

using existing pharmaceutical manufacturing and packaging equipment. The plant is situated in an urban setting with generally flat to slightly hilly terrain and a temperate climate.

d) Locations Where the Product Will Be Used and Disposed Of

- i. Bayer AG, Germany - Acarbose is obtained by fermentation using natural nutrients and a strain of *Actinoplanes utahensis* isolated from coffee plantation soil samples originating from Ruiru, Nairobi, Kenya. No intermediates are used in the production process. Waste from drug substance manufacturing will be collected and treated by recycling, incineration, or biological degradation.
- ii. Bayer, West Haven CT - All returned goods and product packaging waste will be collected for disposal at the West Haven site. Disposal will be managed through the Office of the Manager of Environmental and Safety Affairs, located in West Haven and will consist of incineration via a manifested isolated disposal program. The licensed disposal firm currently contracted by Bayer is

holds a Part A Permit (no expiration date) for hazardous waste treatment, transfer, and recovery with EPA facility identification number MAD053452637. is on Interim Status as a Part B permit facility awaiting final EPA Region 1 approval. This TSDF is situated in an industrial urban setting on the waterfront in the greater

Packaging of the finished tablets will be conducted using the following components:

Bottles:	HDPE with white colorant
Caps:	white and natural polypropylene
Liners:	white lined pulp board
Labels:	printed pressure-sensitive paper
Foil:	film/aluminum foil/ film
Backing:	white, non-plasticized paper/aqueous adhesive/ aluminum foil/vinyl primer/vinyl heat seal coating
Cartons:	printed paper board
Insert:	printed paper

- iii. Patient Population - Precose™ Tablets will be prescribed to Type II diabetics throughout the United States.

5. Identification of the substance that is the subject of the proposed action:

Acarbose, the active ingredient in Precose® tablets, is a naturally occurring pseudotetrasaccharide produced by microorganisms of the genus *Actinoplanes* which are found in soil, water, and riverbanks where decomposing organic material is present. Commercially, acarbose is obtained by

(German Patent 2064092 - June 1, 1983).

Chemical and Physical Properties

INN:	acarbose
CAS Reg. Name:	O-4, 6-Dideoxy-4-[[[1S-(1 α , 4 α , 5 β , 6 α)]-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]- α -D-glucopyranosyl-(1 \rightarrow 4)-O- α -D-glucopyranosyl-(1 \rightarrow 4)-, D-glucose
CAS Reg. No.	56180-94-0
Molecular Weight:	645.63
Molecular Formula:	C ₂₃ H ₄₃ NO ₁₈
SMILES Notation:	CC3OC(OC2O(CO)OC(OC1C(CO)OC(O)C(O)C1O)C(O)C2O)C(O)C(O)C3NC4C=C(CO)C(O)C(O)C4O
Structural Formula:	[See Reference a]
Dissociation Constant:	pK _a = 5.1 (as determined by alkalimetric titration of a hydrochloric 0.02 M acarbose solution)
Partition Coefficient:	log p _{ow} = -3 at 23°C
Water Solubility:	140 g / 100 mL at 20°C
pH:	5.5 - 7.5 (5% aqueous solution)
Melting Point:	Acarbose does not behave characteristically during melting. When the melting point is determined according to the capillary method, sintering can be observed from approximately 160°C. The substance becomes glassy and transparent from approximately 170°C, turns yellow as the temperature increases, and decomposes from

approximately 190°C.

Vapor Pressure: Due to molecular structure and melting behavior, this measurement was not carried out.

Henry's Law Constant: Not applicable.

Specific Gravity: Not applicable.

6. Introduction of Substances into the Environment:

a. Substances to Be Emitted and Controls

- i. **Bayer AG, Germany** - Inorganic material, ion-exchange resins, water, and acarbose may be emitted during manufacture of acarbose drug substance. Liquid wastes from the process and cleaning operations containing water, inorganic material, acarbose, and detergents are collected and transferred to the waste water treatment plant where insoluble material is separated by sedimentation and remaining contaminants are removed by biological degradation. Discharges from analytical operations and solid wastes consisting of filter material and ion-exchange resins are collected and disposed of in incinerator facilities approved for disposal of industrial waste.

Emissions are controlled routinely by the staff of Bayer AG's Department of Environmental Protection (WV-Umweltshutz) to assure compliance with the Federal Emissions Control Act (BlmSchG) of the Federal Republic of Germany. According to this act, each manufacturing installation, regardless of the type of operation, is designated as a single "point source" which may not exceed the established emissions limits. Waste water residues from the point source must be channeled to a specific waste water treatment plant. Water from the treatment plant must meet the requirements for "Treated Water" as laid down in the Decree on the Disposal of Waste Water. According to the Technical Regulations on Waste Control, all solid organic residues resulting from the operation must be incinerated in a facility approved for the disposal of industrial waste. Ash from the incinerator must be disposed of in a licensed landfill.

According to the BlmSchG, the production of pharmaceutical active ingredients is further subject to the Prevention of Harmful Effects on All Compartments of the Environment. Production of substances such as acarbose is specifically addressed in Section 4: Industrial Manufacturing of Materials by Isolation from Biological Products. Articles 4.3 and 4.8 list detailed requirements for facilities engaged in these activities.

- ii. **Bayer, West Haven CT** - No direct emissions of acarbose into the air or onto the land are expected. Solid manufacturing and packaging wastes as well as returned goods will be incinerated by a licensed

disposal firm. Small quantities of acarbose resulting from the cleaning of manufacturing equipment will be emitted into the local sewer system and will be treated at a municipal waste water treatment facility.

b. Compliance with Applicable Emissions Requirements

- i. Bayer AG, Germany - Bayer AG holds all required licenses to manufacture pharmaceutical active ingredients, including acarbose in particular, in its Wuppertal-Elberfeld facilities. The licenses are granted by the Administrative District of Düsseldorf as outlined by the Federal Emissions Control Act. Records of emissions controls carried out are maintained by Bayer AG's Department of Environmental Protection. Production of acarbose drug substance in the Wuppertal-Elberfeld facilities is carried out in full compliance with the Federal Emissions Control Act. The anticipated increase in production volume will not cause emissions in excess of the present licensed limits.
- ii. Bayer, West Haven CT - Wastes from the operation will be managed in such a fashion as to have no significant effect on the facility's compliance status relative to all Federal, State, and local environmental and safety laws and regulations. No modification to any existing permits will be required.

c. Emissions Resulting from Use and/or Disposal of the Product

- i. Bayer AG, Germany - In the event of accidental spillage at the Bayer AG facilities, the drug substance will be collected and destroyed by biological or thermal treatment as described in item 6 or in any other government approved waste water treatment plant or incinerator facility of the public or private sector in Germany.
- ii. Bayer, West Haven CT - Emissions resulting from the disposal of manufacturing wastes and returned goods will be controlled by a properly-licensed disposal firm such as
- iii. Consumers - Approximately 51% and 2% of the dose is excreted in the feces and urine, respectively, as unchanged drug. The major metabolites, formed by interaction with intestinal bacteria and digestive enzymes, have been identified as 4-methylpyrogallol derivatives, i.e., sulfate, methyl, and glucuronide conjugates, and are excreted primarily in the feces.

7. Fate of Emitted Substances in the Environment:

Degradation by Photolysis:

Absorption Spectrum: [See Appendix c]

Direct Photolysis: No direct photolysis reaction, but very slightly sensitive to light (no significant absorption in wavelength above 250 nm as shown in the absorption spectrum).

Hydrolysis Rate Constants: $t_{1/2} > 1$ year at 20°C for pH 5-9
(Approximate value from studies at 50°C)

Studies for a 1% solution at 50°C / 14 days:

pH 4	2.4% hydrolysis
pH 5	2.3% hydrolysis
pH 6	5.4% hydrolysis
pH 7	6.1% hydrolysis
pH 8	16.7% hydrolysis
pH 9	18.8% hydrolysis

Adsorption and Desorption: Adsorption to soil and sediments is not expected due to the high octanol/water partition coefficient and the high water solubility of acarbose.

Biodegradability: 47% DOC-Reduction
(28-day modified OECD Screening Test)

Air - No significant concentrations of substances will be emitted, therefore no significant impact is expected.

Fresh Water, Estuarine, and Marine Ecosystems - No substances will be emitted directly. All waste water will be treated by Bayer AG's own waste water treatment plant or by the West Haven town water treatment plant under State of CT DEP application SP0000141, expiration date 7/31/95 (application renewal filed 2/28/95).

Terrestrial Ecosystems Solid residues, residual packaging, and sewage sludge from the Bayer AG facilities will be incinerated in the company's own incinerator. Ash from the incinerator will be disposed of in a company-owned landfill. Unused bulk packaging, bulk tablet residuals and rejected tablets and dust collected at the Bayer, West Haven CT facilities will be incinerated. The small amounts of inert ingredients remaining in the ash after incineration will pose no threat to a landfill environment.

8. Environmental Effects of Released Substances:

No significant release of substances will occur, therefore no environmental effects of released substances are expected.

Acute Fish Toxicity: LC₀ > 1000 mg/L (96 hr. / *Brachydanio rerio*)

Acute Daphnia Toxicity: EC₀ > 1000 mg/L (48 hr. / *Daphnia magna*)

Acute Bacteria Toxicity: EC₀ > 1000 mg/L (*Pseudomonas putida*)

9. Use of Resources and Energy:

No significant changes in the use of resources and energy at the Wuppertal-Elberfeld or West Haven sites are expected as a result of the proposed action.

No effects are expected upon threatened and/or endangered species and upon property listed in or eligible for listing in the National Register for Historic Places.

10. Mitigating Measures:

No mitigating measures are proposed as no significant environmental effects are expected.

11. Alternatives to the Proposed Action:

An alternative to the proposed action is no action.

12. Preparers:

This assessment was prepared by Gary G. Toczykowski, Manager of Environmental and Safety Affairs at Bayer Corporation, Pharmaceutical Division West Haven CT. He is familiar with the operations to be carried out and is knowledgeable of the wastes to be generated. The following individuals also were involved with preparing various portions of this assessment:

Dr. Karl-Werner Theim - Head of Pharmaceutical Production Group, Environmental and Plant Safety, Bayer AG, Wuppertal, Germany.

Dr. Norman C. Franklin - Head of Quality Systems and Documentation in the Production Department of the Pharmaceutical Division and Chairman of the Validation Steering Committee, Bayer AG, Wuppertal Germany.

The following individuals are responsible for the Bayer AG Report "Investigation of the Ecological Properties of Acarbose":

Prof. Dr. Norbert Caspers
Dipl. Biol. Irene Fenner-Wermbter
Dr. Adolf Grote
Dr. Peter Hartmann
Dr. Reinhard Kanne

Dr. Guenter Mueller
Dr. Andrea Paetz
Dr. Bernd Richter
Dr. Rolf-Dieter Stottmeister

Professional credentials for all of the above are located in Appendix n.

13. Certification:

The undersigned certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm responsible for the preparation of the environmental assessment.

Gary G. Toczykowski Date
Manager of Environmental & Safety Affairs
Bayer Corporation, Pharmaceutical Division

14. References

- a. Merck Index, 11th ed.

15. Appendices

- a. Acarbose Material Safety Data Sheet (MSDS)
- b. Physical and Chemical Properties of Acarbose
- c. Acarbose Absorption Spectrum
- d. Structures of Major Metabolites of Acarbose
- e. Chemical and Biological Degradation of Acarbose
- f. Environmental Effects of Acarbose
- g. Study Report 254 A/91: Ecological Properties of Acarbose
- h. MEEC for the Aquatic Compartment
- i. Federal Requirements (Germany)
- j. Certificate of Compliance - Düsseldorf, Germany)
- k. Regulatory Overview (West Haven CT)
- l. Certificate of Compliance - Bayer, West Haven CT
- m. Description of Clean Harbors Inc. Facility
- n. Curricula Vitae of the Preparers

Appendix A

Acarbose Material Safety Data Sheet (MSDS)

4

DIN Safety Data Sheet

050192/07

Date of issue: October 28, 1991

Page 01 of 04

Company Bayer AG, PH-P Ökologie und Sicherheit
 5600 Wuppertal 1, Telephone: (0202) 367557
 In case of emergency: (0214) 303030 (Werkfeuerwehr Bayer Leverkusen)

Commercial product name Acarbose

1.1 Chemical characterisation: active drug substance
 CAS name: D-Glucose, 0-4,6-dideoxy-4-[[[1S-(1a,4a,5b,6a)]-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]-amino]-α-D-glucopyranosyl-(1→4)-0-α-D-glucopyranosyl-(1→4)-
 CAS-No.: 56180-24-0
 Synonym: Glucobay, Esplanin, Bay g 542v
 1.2 Form: powder
 1.3 Colour: white to yellowish
 1.4 Odour: odourless

2. Physical and safety data tested in accordance with

2.1 Change in physical state:
 Initial melting point: 180 °C decomposition

2.2 Density:
 Bulk density: 150-300 kg/m³

2.3 Vapour pressure:

2.4 Viscosity: not applicable

2.5 Solubility in water: 1400 g/l at 20 °C
 highly soluble

2.6 pH value: ca 6 at 50 g/l water

2.7 Flash point: not applicable

2.8 Ignition temperature:

2.9 Explosive limits:

2.10 Thermal decomposition: No decomposition when used as directed.
 No exothermic reaction without air supply
 (decomposition) up to 200 °C Geigy - test
 No exothermic reaction with air supply
 (spontaneous combustion) up to 115 °C
 Geigy - test
 No exothermic reaction with air supply
 (spontaneous combustion) up to 115 °C
 Geigy - test
 Start of decomposition: 180 °C
 (DTA, heating rate 2 °C/min in Titan)

2.11 Hazardous decomposition products:

2.12 Hazardous reactions: No hazardous reaction when used as directed.
 Dust explosion class: ST 2.
 Geigy test: burning index BZ R 2
 burning index BZ: 2

2.13 Further information:

DIN Safety Data Sheet

050192/07

Date of issue: October 28, 1991

Page 02 of 1

Commercial product name Acarbose

3. Transport

GGVSee/IMDG Code: -- UN No.: -- MFAG: -- EmS: --
 GGVE/GGVS: Class -- No. -- RID/ADR: Class -- No. --
 ADNR: Class -- No. -- Cat -- ICAO/IATA-DGR: NOT RESTR.

Postal dispatch approved: yes

Declaration for land shipment: --

Declaration for sea shipment: --

Other information:

Not dangerous cargo. Keep dry. Avoid heat above +30 °C. Keep separated from foodstuffs.

4. Regulations

No labelling is required in accordance with the German Regulation on Dangerous Substances (GerStoffV) dated August 26, 1986 and corresponding EEC directives.

5. Protective measures, storage and handling

5.1 Technical protective measures:

Protect from moisture.

Transport temperature not more than +40 °C.

Storage temperature not exceeding +30 °C.

Take precautionary measures against static discharges.

Keep away from uninsulated sources of heat.

During handling local official regulations must be observed in order to avert impairment of water by the product.

For storage suitable stores with adequate product-reception volume must be used

5.2 Personal protective equipment:

No special protection required.

5.3 Industrial hygiene:

Wash hands before breaks and at end of work.

To clean the floor and all objects contaminated by this material, use plenty of water.

5.4 Protection against fire and explosion:

Keep away from naked flame.

Do not amp inner sack above vessels containing a mixture of inflammable gases.

In case of fire and/or explosion do not breathe fumes.

5.5 Disposal:

Transport to suitable incinerator.

Sewage containing product residues to be disposed off in suitable incinerator.

DIN Safety Data Sheet

050192/07

Date of issue: October 28, 1991

Page 03 of 04

Commercial product name Acarbose

6. Measures in case of accidents and fires**6.1 After spillage/leakage/gas leakage:**

If larger product quantities are released it may not be allowed to enter into sewage systems, biological sewage treatment plants, surface waters and/or groundwater.

Avoid formation of dust.

Take up mechanically, fill into labelled, closable containers.

Do not let enter into the soil.

Do not rinse into rainwater discharge canal.

To clean the floor and all objects contaminated by this material, use plenty of water.

6.2 Extinguishing media:

All extinguishing materials are suitable.

6.3 First aid:

Contamination of the eyes must be treated by thorough irrigation with water, with the eyelids held open. A doctor (or eye specialist) should be consulted immediately.

6.4 Further information:

Return contained product to the manufacturer.

Combustibility: BZ 2 = brief ignition and rapid extinction.

Keep away from naked flame.

Cool undamaged containers with water.

In fire-fighting observe fire classification A.

In case of fire NDx may develop.

In case of fire care must be taken to collect the quenching water.

7. Information on toxicity

Industrial usage with the usual precautions of industrial hygiene no effects detrimental to health are known.

Acute toxicity:

LD₅₀ oral, rat: 15000 mg/kg

LD₅₀ oral, dog: 10000 mg/kg

LD₅₀ intravenous, mouse: 8000 mg/kg

Ames-test: negative

Chemical-pharmacological effect: Antidiabetic

8. Information on ecological effects

Correct handling will produce no environmental problems.

Fish toxicity: Test solution: 1 g/l

Zebra barbel (Brachydanio rerio) LC₅₀: >1000 mg/l 96h

Toxicity for Daphnia: Test solution: 1 g/l

EC₅₀: >1000 mg/l

Growth-inhibition:

Pseudomonas putida: no inhibition to 1000 mg/l.

Escherichia coli: no inhibition to 1000 mg/l.

Biological degradability: 47% (28 days) (Modified OECD Screening Test)

DIN Safety Data Sheet

050192/07

Date of issue: October 28, 1991

Page 04 of 04

Commercial product name Acarbose

8. Information on ecological effects (Continuation)

According to the present state of knowledge no disturbance is caused in biological sewage treatment plants if the product is used properly. Do not allow to enter surface waters or groundwater.

Hazard class (WGK): 1 - slightly hazardous to water
(own classification)

WGK = Classification in accordance with the German Water Resources Act

9. Further information

All tests to the above mentioned data are based on methods generally used in the FRG.

The instructions given here are valid only for the product as supplied, not for derivatives resulting from its use.

BAYER-Storage class: 9

(8 if there is a large proportion of readily flammable packing materials)

The data given here is based on current knowledge and experience. The purpose of this Safety Data Sheet is to describe the products in terms of their safety requirements. The data does not signify any warranty with regard to the products' properties.

Appendix J

**Certificate of Compliance from the Government of Düsseldorf, Germany
For Production of Acarbose in Bayer AG Wuppertal-Elberfeld Facilities**

**Glucobay[®] (Acarbose) Drug Substance
Environmental Assessment**

9.61 - 1

**Certificate of Compliance
Administrative District of Düsseldorf, Germany**

Furthermore, the intended project shall not contravene other public laws, in particular those concerned with the conservation of nature, country-side and waters.

Before granting a license all relevant environmental requirements shall be checked in conjunction with the competent authority. Thus establishing that the valid requirement had been fulfilled at the time of grant the license.

The production plant shall also be subject to special supervision by the "State Environmental Protection Authorities" (Landes Umweltbehörden) in particular by the Trades Inspectorate of North Rhine Westphalia (Staatliche Gewerbeaufsichtsamt), Wuppertal responsible for the enforcement of the act, and which is under my jurisdiction.

To my knowledge no complaints have been reported.

Yours faithfully

Woog

Signed for and on behalf of the President of the Regional Administration

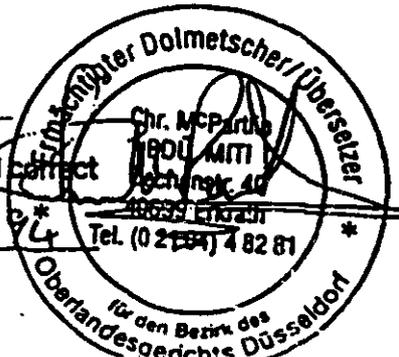
Stamp of the office of the President of Regional Administration

Certified signature Administration clerical officer

Ermächtigt
*
Ober.

Certified as a true and correct translation

21-3-84



Appendix L

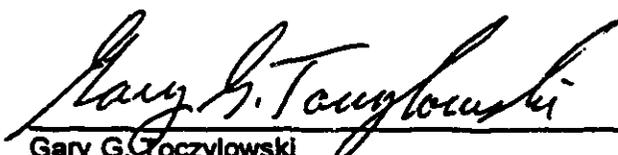
**Certificate of Compliance
Bayer Corporation, Pharmaceutical Division
West Haven CT**

Environmental and Safety Compliance Statement

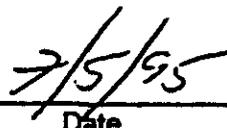
Bayer Corporation
Pharmaceutical Division
400 Morgan Lane
West Haven, CT

As applicable to the production of *Precose*® (acarbose tablets) 50 mg and 100 mg at its facilities in West Haven, CT, Bayer Corporation states that it is in compliance with all environmental and safety emissions requirements set forth in permits as well as federal, state, and local statutes and regulations.

Furthermore, there are currently no pending environmental or safety consent decrees and/or administrative orders against these facilities concerning any emissions standard.



Gary G. Toczyłowski
Manager, Environmental and Safety Affairs


Date

*****SENSITIVE*****

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-482

PRECOSE™ (ACARBOSE TABLETS)

50 and 100 mg

REVIEW DIVISION: HFD-510

CENTER FOR DRUG EVALUATION AND RESEARCH

HFD-004

DATE COMPLETED: August 17, 1995

ENVIRONMENTAL ASSESSMENT

1. Date:

NDA submitted: September 2, 1994
Consult to HFD-102: September 22, 1994
EA review #1: May 30, 1995
Revised EA dated: July 5, 1995
EA review #2: July 28, 1995
Amendment: August 10, 1995*

*Information reviewed.

CSO: John Short

2. Name of Applicant/Petitioner:

Bayer Corporation
Pharmaceutical Division

3. Address:

400 Morgan Lane
West Haven, CT 06516

RESPONSE TO DEFICIENCY LETTER OF August 9, 1995:

- (1) The MEEC reported in section 6.c has not been revised to reflect the revised calculation provided in Appendix H. Release of production estimates or MEEC's is not mandatory in the FOI'able EA as this may be classified as confidential business information. You can either choose to delete this information from the FOI'able copy (provide a replacement page 03-03B-0000007 and a statement that you are designating appendix H as confidential) or revise the document to consistently report the MEEC (provide a replacement page 03-03B-0000007).

RESPONSE: Replacement pages with the MEEC deleted have been provided. **ADEQUATE**

- (2) It should be indicated (Section 9) whether any effects are expected upon threatened and/or endangered species and upon property listed in or eligible for listing in the National Register of Historic Places. A replacement page or an addendum to the FOI'able EA may be submitted with this information, whichever is more convenient.

RESPONSE: A replacement page with the statement has been included. **ADEQUATE**

SUMMARY

The maximum expected environmental concentration is 3.9×10^{-4} ppm. The NOEC were > 1000 ppm for fish (*Brachydanio rerio*), *Daphnia magna* and bacteria (*Pseudomonas putida*). These are greater than 6 orders of magnitude higher than the MEEC. No environmental impacts would be expected. A FONSI should be written.

*FAX'd Definitions
to Baze on 8/1/95
Baze responded
8/10/95 -
Sent (hard copy)
to HFD-005 on 8/11/95*

SENSITIVE

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-482

PRECOSE™ (ACARBOSE TABLETS) 50/100 MG

REVIEW DIVISION: HFD-510

CENTER FOR DRUG EVALUATION AND RESEARCH

HFD-004

DATE COMPLETED: 28 JULY 1995

ENVIRONMENTAL ASSESSMENT

1. **Date:**

NDA submitted: September 2, 1994
Consult to HFD-102: September 22, 1994
EA review #1: May 30, 1995
Revised EA dated: July 5, 1995
CSO: John Short

2. **Name of Applicant/Petitioner:**

Bayer Corporation
Pharmaceutical Division

3. **Address:**

400 Morgan Lane
West Haven, CT 06516

RESPONSE TO DEFICIENCY LETTER OF MAY 30, 1995:

4. **Regarding Section 4, Description of the proposed action:**

A. **Requested Approval:**

The description of the proposed action in Section 4 of the EA for the product should state that the action includes manufacturing and packaging of the drug product, and should include the NDA number.

RESPONSE: The requested changes have been made.
Adequate.

B. **Production Locations:**

- i. **Proprietary Intermediate(s):** Proprietary intermediates are not discussed in the documentation concerning the manufacture of the drug substance. Please clarify whether proprietary intermediates are used in the process, please confirm that these intermediates are not manufactured at another location. If proprietary intermediates are manufactured at another location, that location must be addressed in the EA.

NDA 20482

PRECOSE

3 OF 3

RESPONSE: The sponsor has included text stating that no intermediates are used in the production process. Adequate.

- ii. Drug substance: Please provide the building number and the street in the business address.

RESPONSE: The address of the Bayer facility that will produce the drug substance is provided as Buildings 150b, 152a, 152b, and 153, 21-399 Freidrich Ebert Strasse, Wuppertal, Germany, D-42096. A brief description of environment at and surrounding the facility is provided. Adequate.

- iii. Finished Dosage Form: No information concerning the packaging process for the drug is included. Please provide this information.

RESPONSE: The sponsor indicates that packaging of the finished tablets will use the following components:

Bottles: HDPE with white colorant
Caps: white and natural polypropylene
Liners: white lined pulp board
Labels: printed pressure-sensitive paper
Foil: film/aluminum foil/ film
Backing: white, non-plasticized paper/aqueous adhesive/aluminum foil/vinyl primer/vinyl heat seal coating
Cartons: printed paper board
Insert: printed paper

The sponsor also stated that product packaging waste will be collected for disposal at the West Haven site. Disposal will be managed through the Office of the Manager of Environmental and Safety Affairs, located in West Haven and will consist of incineration via a manifested isolated disposal program. Adequate.

- 5. Regarding Section 5, Identification of the chemical substances that are the subject of the proposed action:

products but this additional information was requested to be included in the revised EA, if available).

RESPONSE: The sponsor indicates that this information is not available. Adequate.

6. Regarding Section 12, List of preparers and their qualifications:

The preparers of the drug substance portion of the EA are identified, but their expertise, experience, and professional disciplines are not described. Consultants used in the conduct of test studies are identified, but their expertise, experience, and professional disciplines are not included. Provide this information.

RESPONSE: The preparers of the EA are identified and their expertise, experience and professional disciplines are provided in curriculum vitae in Appendix N. All preparers and consultants are employees of the Bayer firm. Adequate.

7. Regarding the submission of a revised EA:

The environmental assessment should be one document incorporating both the drug substance and drug product. Please revise the EA to include both.

RESPONSE: In response to this comment, the sponsor has provided separate confidential and non-confidential versions of the EA. The two versions differ only in the absence of confidential appendices O through Q in the non-confidential version.

Confidential appendix O contains a description of the components of the tablets. Confidential appendix P, entitled "Report 7125: Characteristics of Acarbose", contains hygroscopic measurements, stability data, and other physical and chemical data about the drug substance. Confidential appendix Q contains Bayer AG Report R-4775: Pharmacokinetics of Acarbose. Relevant information contained in these appendices is summarized in the body of the EA that is available to the public.

Adequate.

In addition to the changes made in response to FDA's request for more information, the sponsor has also made the following additional changes to the EA:

1. Regarding Section 1, Environment Assessment, the name of the sponsor has been changed from Miles Inc. to Bayer Corporation, effective April 3, 1995.

REVIEWER NOTES: This name change reflects recent corporate realignments between Miles Inc. and the Bayer Corporation. Adequate.

2. Regarding Sections 4(d), 6(a), and 6(b), a letter provided by the sponsor indicates that information on consumer use has been added to these sections.

REVIEWER NOTES: The reviewer found additional information in Section 4(d) that stated that Precose™ Tablets will be prescribed to Type II diabetics throughout the United States. Adequate. However, review of Section 6(a) and 6(b) showed that these sections did not concern consumer use but rather emissions, controls and compliance with emission requirements at the Germany and Connecticut facilities. However, information concerning excretion of the drug is described in Section 6(c). Information concerning consumer use of the drug appears to be adequate for the purposes of the environmental assessment. Adequate.

3. Regarding Section 4(d)ii and Appendix M, information, including EPA status, concerning the licensed disposal firm, has been added to the EA.

REVIEWER NOTES: Section 4(d)ii states that _____ is the licensed disposal firm currently contracted by Bayer. The EA states that _____ holds a Part A Permit (no expiration date) for hazardous waste treatment, transfer, and recovery (EPA facility identification number MAD053452637). _____ is on Interim Status as a Part B permit facility awaiting final EPA Region 1 approval. A brief description of the environment surrounding the _____ facility is also provided.

Appendix M recounts this same information about the _____ facility and also describes the facility's incineration process. The incineration process includes second stage combustion temperatures in excess of 2000 degrees Fahrenheit and controls to prevent volatile and acid gas discharge.

Adequate.

4. Regarding Appendix K, permit numbers and expiration dates have been added to the list of applicable laws and regulations.

REVIEWER NOTES: The information was provided. Adequate.

5. Regarding Section 6(c)ii and Appendix H, the has been deleted and the MEEC has been recalculated using a maximum daily dose based on 100 mg t.i.d.

REVIEWER NOTES: The references to the dose have been deleted from the EA. In Appendix H, the sponsor correctly calculated the MEEC, using the anticipated yearly production based on the highest (100 mg t.i.d.) dosage, to be 3.9×10^{-4} ppm. However, the summary portion of the EA contradicts the information in the appendix and reports the MEEC as 7.8×10^{-4} ppm. This higher value is the same as that reported in the initial submission of the EA and is based on the discontinued **DEFICIENT**. The sponsor should correct the text in the summary portion of the EA to portray a consistent value for the MEEC based on the highest proposed dosage.

6. Regarding Appendix A, a material safety data sheet for the drug substance has been added.

REVIEWER NOTES: The information was provided in non-confidential Appendix A. Adequate.

7. The order and grouping of the appendices has changed due to the combining of the drug substance and drug product sections of the EA and the creation of the FOIable EA.

REVIEWER NOTES: Adequate.

GENERAL ISSUE: This application qualifies for an abbreviated EA under 21 CFR.31a(b)(5).

REQUEST FOR ADDITIONAL INFORMATION: For portions of Section 9, the sponsor has not provided all of the information required by this abbreviated format. The sponsor has provided adequate information concerning the resources and energy requirements for the production of the drug product but has not addressed the effects, if any, upon threatened and/or endangered species and upon property listed in or eligible for listing in the National Register of Historic Places. The sponsor should provide a brief statement about the anticipated effect of the drug production upon these species and property. **DEFICIENT**

SUMMARY:

The Agency has received the sponsor's response to the 30 May 1995 review of the EA assessment. This correspondence consisted of the following items:

- (1) A listing of each review comment followed by a statement providing information about that comment and describing resultant changes to the EA.
- (2) A summary of some additional changes made to the EA.
- (3) Revised non-confidential and confidential versions of the EA.

Regarding the sponsor's response to the 30 May 1995 comments, review of this response showed that the information provided was adequate to address all comments, but several minor issues remain.

DRAFT DEFICIENCY LETTER

- (1) The MEEC reported in section 6.c has not been revised to reflect the revised calculation provided in Appendix H. Release of production estimates or MEEC's is not mandatory in the FOI'able EA as this may be classified as confidential business information. You can either choose to delete this information from the FOI'able copy (provide a replacement page 03-03B-0000007 and a statement that you are designating appendix H as confidential) or revise the document to consistently report the MEEC (provide a replacement page 03-03B-0000007).
- (2) It should be indicated (Section 9) whether any effects are expected upon threatened and/or endangered species and upon property listed in or eligible for listing in the National Register of Historic Places. A replacement page or an addendum to the FOI'able EA may be submitted with this information, whichever is more convenient.

SHORT

DIVISION COPY

MAY - 1 1995

SENSITIVE

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-482

PRECOSE® (ACARBOSE) TABS ORAL 50/100/200 MG

REVIEW DIVISION: HFD-510

CENTER FOR DRUG EVALUATION AND RESEARCH

HFD-004

DATE COMPLETED: 03/03/95

Item conveyed in letter dated 5/30/95
Response dated 7/5/95
Sent for consult 7/10/95 (expect complete consult 8/14/95)

ENVIRONMENTAL ASSESSMENT

1. Date:

EA dated: August 4, 1994
NDA submitted: September 2, 1994

Consult #1
to HFD-102: September 22, 1994

Assigned: January 25, 1995

CSO: John Short

2. Name of Applicant/Petitioner:

Miles Incorporated
Pharmaceutical Division

Adequate.

3. Address:

400 Morgan Lane
West Haven, CT, 06516

Adequate.

4. Description of the proposed action:

a. Requested Approval:

Miles Inc., has filed an NDA for manufacturing of the drug substance, acarbose, and manufacturing and packaging of the drug product, Precose® (acarbose 50, 100, tablets).

The description of the proposed action in Section 4 of the EA for the drug product should state that the action includes manufacturing and packaging of the drug product, and should include the NDA number. **DEFICIENT.**

b. Need for Action:

The product will be used in the treatment of non-insulin dependent diabetes mellitus. Adequate.

c. Production Locations:

i. Proprietary Intermediate(s):

Proprietary intermediates are not discussed in the documentation concerning the manufacture of the drug substance. The submitter should clarify whether proprietary intermediates are included in the manufacturing process. If proprietary intermediates are used in the process, the submitter should confirm that these intermediates are not manufactured at another location. If proprietary intermediates are manufactured at another location, that location must be addressed in the environmental assessment (EA).

INFORMATION REQUEST.

ii. Drug Substance:

The principal materials used in the manufacture of Glucobay (acarbose) are listed. The drug substance will be manufactured at the Bayer AG Wuppertal-Elberfeld facilities, 217-399 Friedrich Ebert Street, Wuppertal, Germany, D42096. However, the building number and street are not provided in the business address of the submitters of the EA. This address is listed only as Bayer AG Pharma Production, Leverkusen, Germany, 51368. Provide the complete address for this business location.

DEFICIENT.

iii. Finished Dosage Form:

The principal components of Precose® tablets are provided. The drug product will be manufactured at Miles Inc. Pharmaceutical Division, 400 Morgan Lane, West Haven, CT, 06516. However, no information concerning the packaging process for the drug product is included in the EA. Provide information about the type of packaging proposed for the drug product.

EA Review #1, NDA 20-482

Page 5

DEFICIENT.

d. **Expected Locations of Use (Drug Product):**

Precose® Tablets will be prescribed to individuals throughout the United States.

Adequate.

e. **Disposal Locations:**

Product and packaging wastes will be sent to the West Haven site for disposal. The Office of the Manager of Environmental and Safety Affairs in West Haven will manage the incineration of these wastes through a manifested isolated disposal program.

Licensed disposal firms contracted by Miles were

ADEQUATE.

5. **Identification of chemical substances that are the subject of the proposed action:**

Drug Substance: Glucobay (acarbose)
Chemical Name: D-Glucose, O-4,6-dideoxy-4-[[4,5,6 trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]- α -D-glucopyranosyl-(1-4)-, O- α -D-glucopyranosyl-(1-4)-, [1 α , 4 α , 5 β , 6 α]-
CAS #: 56180-94-0
Molecular Weight: 645.63
Molecular Formula: C₂₅ H₄₃ N O₁₈
Structural Formula: Provided. (See EA, Appendix 1)

Physical Descrip.: White to slightly yellow powder
Additives: Starch, microcrystalline cellulose NF,
colloidal silicon dioxide NF, and
magnesium stearate NF are identified as
the additives.
Impurities:

ADEQUATE/INFORMATION REQUEST, IF AVAILABLE.

6. **Introduction of substances into the environment: For the
site(s) of production:**

This application qualifies for an abbreviated EA under 21
CFR 25.31a(b)(5) and the format requirements pertain.

A letter from the appropriate German authority is sufficient
for item 6 along with the information provided by the firm.

a. **Potential Emitted Substances:**

In the manufacture of the drug substance in Germany,
inorganic material, ion-exchange resins, water and
acarbose may be emitted. Liquid wastes from the
process and cleaning operations will be sent to a waste
water treatment plant governed by the "Decree on the
Disposal of Waste Water." Solid wastes will be
disposed in incinerator facilities governed by the
"Technical Regulations on Waste Control." Production
is carried out in compliance with the "Federal
Emissions Control Act." The discussion is adequate.

b. Controls (Air, Liquid Effluent, Solid):

The document states that the wastes from the production of the drug product will not exceed existing permits but does not provide any specific information on the controls to prevent discharge of air, liquid or solid, or to address occupational safety and health regulations.

ADEQUATE.

c. Compliance with Federal, State and Local Emission Requirements:

For the drug substance, a copy of the letter from the Office of the President of the Regional Administration of the "State Environmental Protection Authorities" confirming the issuance of license 55.8851-8859/3193 dated March 20, 1989 to produce the drug substance is provided. Adequate.

For the drug product, an environmental and safety compliance statement for the manufacturing and packaging is provided and the federal, state and local statutes and regulations that are applicable to the operation are identified. Adequate.

d. Effect of Approval on Compliance with Current Emissions Requirements:

The document states that there will be no effect on compliance with current emissions requirements. Adequate.

e. Estimated Expected Emitted Concentration/Quantities:

A calculation of the maximum expected emitted concentration of acarbose or any single metabolite is provided. MEFC is 7.8×10^{-4} ppm for the aquatic compartment. Adequate.

7. Fate of emitted substances in the environment:

Parent Compound: Acarbose

In vivo: Acarbose
Metabolites: 4-methylpyrogallol derivatives and glucuronide conjugates.

The majority of the parent compound is excreted unchanged. A radioactive pharmacokinetic clinical study for rats, dogs, and man is included in the confidential appendix. Adequate.

Tier 0 attributes:

Tier testing is minimal for a natural product EA. Most information may be inferred from the scientific literature or reasonable deduction from similar naturally occurring substances. The doctrine of "rule of Reason" should apply here with this class of drug.

Water solubility of the drug substance was reported as 140 g/100 ml in Appendix D. Study results indicate that the submitter has performed analysis to confirm that the water solubility of the drug substance exceeds 60g/100ml. Both these values for water solubility exceed the Tier 1 threshold.

Hydrolysis was determined by incubation of a 1% solution of the drug substance at 50°C for 14 days at pH 4, 5, 6, 7, 8, and 9. The data were interpreted to provide an approximation of a half-life >1 year at 20°C for pH 5 through 9. The rates of hydrolysis are below the Tier 0 threshold indicating that hydrolysis is not a primary removal mechanism.

A dissociation constant of 5.1 was determined by alkalimetric titration, and formal communication from an industry scientist provided a dissociation constant of 4.9.

An octanol-water partition value of -3 at 23°C is reported. This low octanol-water partition value is below the Tier 2 threshold.

The values for vapor pressure and Henry's Law constant were not included because heating of the compound caused decomposition at temperatures below the vaporization point. Adequate.

ADEQUATE.

Tier 1 Attributes (see Attachment 2)

Aerobic biodegradation of the drug substance in water was tested. Biogradation did not exceed the 60% criteria for the 28 day test period. The substance is categorized as not readily degradable. Adequate.

The ultraviolet spectrum, 300 through 200 nm, was provided in .01N NaOH, .01N HCl, water, and in buffer solutions at pH 5 through 8. No maxima was noted in the .01N HCl and water solutions. An absorbance maxima was noted at 210 nm in the alkaline solution confirming studies indicating hydrolysis under alkaline conditions. The lack of absorbance maxima in the ultraviolet regions indicates that drug substance is not readily susceptible to photodegradation. Adequate.

Testing of the aqueous photodegradation of the drug substance was performed. The tests indicate that the drug substance is stable in normal daylight for 7 days. Significant photodegradation occurred upon exposure to UV light at 254 nm for 16 hours. The study results indicate that the drug substance is not readily photodegradable. Adequate.

8. Environmental effects of released substances

Results from the microbial inhibition testing were provided. These results indicate an EC 0 value of >1000 mg/l.

Acute aquatic toxicity testing was conducted using an invertebrate (Daphnia). No adverse effects were noted for the 48 hour testing period. The EC 0 value was reported to be \geq 1000 mg/l. Adequate.

Acute aquatic toxicity testing was conducted using a vertebrate (Zebra fish-Brachydanio rerio). No adverse effects were noted for the 96 hour testing period. The LC 0 value was reported to be \geq 1000 mg/l. Adequate.

Items 9, 10, 11, and 15 are not ordinarily required for an abbreviated EA.

12. List of preparers, & their qualifications (expertise, experience, professional disciplines) and consultants:

The preparers of the Drug Product EA are identified and their qualifications are presented in curriculum vitae. The preparers of the drug substance portion of the EA are identified but their expertise, experience and professional disciplines are not described. Consultants used in the conduct of test studies are identified but their expertise, experience and professional disciplines are not included.

DEFICIENT.

13. Certification:

Provided. Adequate.

14. References:

One reference, to the Merck Index, is provided. The list of references should include all materials referred to and used in the preparation of the EA, including formal scientific communications and state, local, and federal regulations.

ADEQUATE.

DRAFT DEFICIENCY LETTER

1. General Issues:
2. Regarding Section 4, Description of the Proposed Action:
 - a. Requested Approval: The description of the proposed action in Section 4 of the EA for the drug product should state that the action includes manufacturing and packaging of the drug product, and should include the NDA number.
 - b. Production Locations:
 - i. Proprietary intermediate(s): Proprietary intermediates are not discussed in the documentation concerning the manufacture of the drug substance. The submitter should clarify whether proprietary intermediates are included in the manufacturing process. If proprietary intermediates are used in the process, the submitter should confirm that these intermediates are not manufactured at another location. If proprietary intermediates are manufactured at another location, that location must be addressed in the EA.
 - ii. Drug Substance: The building number and the street are not provided in the business address of the submitters of the EA.
 - iii. Finished Dosage Form: No information concerning the packaging process for the drug is included.
3. Regarding Section 5, Identification of chemical substances that are the subject of the proposed action: Component II is identified by formula as a degradation product formed by the removal of glucose from the drug substance. No CAS number or chemical name is provided for Component II. Component IV, also a degradation product, is not identified by formula, chemical name or CAS number in the document. This information should be included if available.

4. Regarding Section 12, List of Preparers and their qualifications: The preparers of the drug substance portion of the EA are identified but their expertise, experience and professional disciplines are not described. Consultants used in the conduct of test studies are identified but their expertise, experience and professional disciplines are not included.
5. The environmental assessment should be one document incorporating both the drug substance and drug product.

MICROBIOLOGY REVIEW

**Not Applicable Because This Is
A Tablet Formulation**

NDA 20-482

JUL 18 1995

Bayer Corporation
Attention: Mr. Bill Maguire
Associate Director, Training and Surveillance
400 Morgan Lane
WEST HAVEN CT 06516-4175

*Revised
7/29/95
OK*

Dear Mr. Maguire:

Please refer to your pending September 2, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Precose (acarbose) 50, 100, Tablets.

We have completed our review of the biopharmaceutics section of your submission and have identified the following deficiencies:

We recommend that the following dissolution method and specification be used for Precose tablets:

Apparatus Type:

Media:

Speed of Rotation:

Sampling Time:

Recommended Specifications:

Please provide an amendment to the NDA as soon as possible.

If you have any questions, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

JRS 7/27/95
Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

JUL 12 1995

Bayer Corporation
Attention: Mr. Bill Maguire
Associate Director, Training and Surveillance
400 Morgan Lane
WEST HAVEN CT 06516-4175

Dear Mr. Maguire:

Please refer to your pending September 2, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Precose (acarbose) 50, 100, Tablets.

We also refer to your amendments dated June 16 and 27, 1995, providing for revisions in the package insert.

The June 16 version of the package insert and subsequent revisions made by FDA staff and transmitted to you by telefacsimile on June 21, 1995, were discussed at a meeting between Bayer representatives and FDA staff on June 22, 1995. Many revisions were agreed upon at that meeting, and your amendment of June 27 provided additional revisions. If we have further comments about the latter revision, they will be forwarded to you at a later time.

At this time we are commenting on the additional indications which you included in the June 16 version of the package insert. In that submission you revised the sentence, "PRECOSE may also be used in combination with sulfonylurea therapy", to:

~~PRECOSE may also be used in combination with sulfonylurea, metformin, or insulin therapy to further enhance glycaemic control therapy. [Redlining added and strikethrough deleted.]~~

From a regulatory perspective, adding this constitutes the addition of new indications. FDA's policy is that an additional indication(s) cannot be added to a pending NDA. If one chooses to add another indication for use of the drug while an NDA is pending, a separate NDA may be filed, or one may submit a supplement following approval of the NDA.

This policy was discussed at the June 22, 1995 meeting, and you agreed to delete these indications from the INDICATIONS AND USAGE Section of the package insert (which was done in the June 27 amendment) and submit a supplement if the NDA is approved.

If you have any questions, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

JS 7/11/95
Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Original NDA 20-482
HFD-510/Div. Files
DISTRICT OFFICE
HFD-510/CSO/J.R.Short
HFD-510/RMisbin, AFleming, EGalliers

drafted: JShort/6/30/95/N20482AD,JRS
r/d Initials: EGalliers 7/5, RMisbin 7/6, AFleming 7/10/95
final: js/7/11/95

ADVICE LETTER (AD)

JShort
7/11/95

NDA 20-482

MAY 30 1995

Bayer Corporation
Attention: Mr. Bill Maguire
Associate Director, Training and Surveillance
400 Morgan Lane
WEST HAVEN CT 06516-4175

*Response dated
7/27/95 and forwarded
for comment 7/10/95*

Dear Mr. Maguire:

Please refer to your pending September 2, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Precose (acarbose) 50, 100, Tablets.

We have completed our review of the pharmacology and environmental assessment sections of your submission and have identified the following deficiencies:

Environmental Assessment (EA)

1. Regarding Section 4, Description of the Proposed Action:

a. Requested Approval:

The description of the proposed action in Section 4 of the EA for the drug product should state that the action includes manufacturing and packaging of the drug product, and should include the NDA number.

b. Production Locations:

- i. Proprietary intermediate(s): Proprietary intermediates are not discussed in the documentation concerning the manufacture of the drug substance. Please clarify whether proprietary intermediates are included in the manufacturing process. If proprietary intermediates are used in the process, please confirm that these intermediates are not manufactured at another location. If proprietary intermediates are manufactured at another location, that location must be addressed in the EA.
- ii. Drug Substance: Please provide the building number and the street in the business address.
- iii. Finished Dosage Form: No information concerning the packaging process for the drug is included. Please provide this information.

2. Regarding identification of chemical substances that are the subject of the proposed:

3. Regarding Section 12, List of preparers and their qualifications:

The preparers of the drug substance portion of the EA are identified, but their expertise, experience, and professional disciplines are not described. Consultants used in the conduct of test studies are identified, but their expertise, experience, and professional disciplines are not included. Please provide this information.

4. The environmental assessment should be one document incorporating both the drug substance and drug product. Please revise the EA to include both.

Pharmacology

Although package insert (PI) comments will be communicated to you in their entirety following our internal labeling meeting scheduled for June 6, 1995, we offer the following comments at this time regarding the PRECAUTIONS Section:

1. Subsection "Carcinogenesis, Mutagenesis, and Impairment of Fertility":
 - a. Replace the sentence, "Acarbose treatment resulted . . . renal tumors (renal adenomas/carcinomas)" with "Acarbose treatment resulted in a significant increase in the incidence of renal tumors (adenomas and adenocarcinomas) and benign Leydig cell tumors."
 - b. Delete the following paragraph: "On the basis of these studies, it was concluded that acarbose has no carcinogenic potential."
 - c. Delete the following sentences from the paragraph beginning "The mutagenic potential . . .": "Samples of urine and lymphocytes from humans treated with acarbose for up to six year were tested in vitro for point mutations and chromosomal damage" and "Negative responses were also obtained with samples from long-term human recipients of PRECOSE therapy with the Salmonella/Microsome test in urine and the Human Peripheral Blood Lymphocyte Analysis."
2. Subsection "Pregnancy" and subheading "Teratogenic Effects":

The dose multiples of 48 and 54 seem to be based on mg/kg doses instead of on drug blood levels. The high dose was 480 mg/kg in the teratology studies and the highest

recommended dose in patients is approximately 10 mg/kg. Based on the AUC's of total radioactivity given in the acarbose ADME Technical Summary in Vol. 8, a multiple of 9 would seem more appropriate.

Please do NOT submit a revised PI with these corrections until you receive our comments on the entire PI.

Please respond to the EA concerns as soon as possible.

If you have any questions, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

MS/30/95
Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-482
HFD-510/Div. Files
DISTRICT OFFICE
HFD-004/RJerussi
HFD-003/MJones
HFD-102/PVincent
HFD-510/CSO/J.R.Short
HFD-510/AJordan, MAnec, YKChiu

drafted: JShort/May 11, 1995/N20482IR.3JS
r/d Initials: AJordan 5/11/95 (EA staff did not want to sign off)
final: JShort 5/26/95

INFORMATION REQUEST (IR)

Platt
5/26/95

NDA 20-482

Swire
APR 11 1995

Bayer Corporation
Attention: Mr. Bill Maguire
Associate Director, Training and Surveillance
400 Morgan Lane
WEST HAVEN CT 06516-4175

Dear Mr. Maguire:

Reference is made to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Precose (acarbose) 50, 100 Tablets.

We have following additional request regarding the Pharmacokinetics portion of your application:

You are seeking approval of 50, 100, mg tablet strengths which are not proportionally similar in ingredients. Normally, in a situation such as this, the sponsor would be required to demonstrate bioequivalency/dose proportionality between the different dosage strengths. However, because the site of action for this compound is within the gastrointestinal tract, the use of systemic levels of drug may not be that informative or relevant. Therefore, more rigorous comparative in vitro dissolution testing is needed in order to support the approval of these different tablet strengths. Approval of these tablet strengths will require adequate data from comparative dissolution studies on the 50, 100, tablets utilizing simulated gastric fluid without enzymes, simulated intestinal fluid without enzymes, water and other media as appropriate using 12 dosage units per lot involving more than one time point (e.g., 5, 10, 15, 30, and 60 minutes) for those lots used in the pivotal bioavailability and clinical trials. In addition, a pH solubility profile of the drug should be submitted.

This information should be submitted as soon as possible so that the Biopharmaceutics review will not be delayed.

Should you have any questions in regard to these requests, please contact Mr. John Short at 301-443-3510.

Sincerely yours,

JS 4/11/95
Solomon Sobel, M.D.
Director

Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Shen 2

NDA 20-482

JAN 17 1995

Miles Laboratories
Attention: C. Christine Miller, Pharm.D.
Associate Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Dr. Miller:

Reference is made to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Precose (acarbose) 50, 100, Tablets.

We have completed our initial screening of the Human Pharmacokinetics and Bioavailability section (Item 6) of your application and request the following information:

1. Because several formulations were utilized in the clinical studies submitted with this NDA, please identify which formulations were used in which clinical trials.
2. Please provide in vitro dissolution data for all formulations utilized in clinical trials.
3. Please evaluate available pharmacokinetic data based upon gender, race, and body weight.

than the 50 and 100 mg tablets in the dissolution studies, an additional bioequivalence study may be needed.

This information should be submitted as soon as possible so that the Biopharmaceutics review will not be delayed.

Should you have any questions in regard to these requests, please contact Mr. John Short at 301-443-3510.

Sincerely yours,

JS 1-15-95

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

Short

NDA 20-482

SEP - 8 1994

Miles Laboratories
Attention: C. Christine Miller, Pharm.D.
Associate Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Dr. Miller:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Precose (acarbose) 50, 100.	Tablets
Therapeutic Classification:	S	
Date of Application:	September 2, 1994	
Date of Receipt:	September 6, 1994	
Our Reference Number:	NDA 20-482	

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 5, 1994, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact:

Mr. John R. Short
Consumer Safety Officer
(301) 443-3510

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

LUP
FOR

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

cc: Orig. NDA
HFD-510
DISTRICT OFFICE
HFD-510/JShort 9/8/94 \N20482AC.JRS

ACKNOWLEDGEMENT - AC

J Short
9/18/94

END

A handwritten signature in black ink, consisting of several loops and a trailing flourish, positioned above a horizontal line.

J.H.M. RESEARCH & DEVELOPMENT, INC. 5776 SECOND STREET, N.E. WASH. DC 20011