CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 20482/S007/S008

Trade Name: PRECOSE TABLETS

Generic Name: ACARBOSE

Sponsor: BAYER PHARMACEUTICAL DIVISION

Approval Date: 09/29/98

Indication(s): COMBINATION TREATMENT USE OF PRECOSE FOR PATIENTS WITH TYPE 2 DIABETES TREATED WITH DIET PLUS INSULIN, AND COMBINATION TREATMENT USE OF PRECOSE FOR PATIENTS WITH TYPE 2 DIABETES TREATED WITH DIET PLUS METFORMIN

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20482/S007/S008

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter				X
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20482/S007/S008

APPROVAL LETTER

NDA 20-482/S-007 and S-008

SEP 29 1998

Bayer Pharmaceutical Division
Attention: Richard J. Fanelli, Ph.D.
Associate Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Dr. Fanelli:

Please refer to your supplemental new drug applications dated September 29, 1997 (S-007), received September 30, 1997, and November 24, 1997 (S-008), received November 25, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Precose® (acarbose) Tablets.

We acknowledge receipt of your submissions dated October 20, 1997, for S-007, and February 13 and July 7, 1998, for both S-007 and S-008. The user fee goal dates are September 30, 1998 (for S-007), and November 25, 1998 (for S-008).

These supplemental new drug applications provide for the new combination use of Precose for patients with type 2 diabetes treated with diet plus insulin (S-007) and for the new combination use of Precose for patients with type 2 diabetes treated with diet plus metformin (S-008).

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

The final printed labeling (FPL) must be identical to the submitted labeling (text for the package insert dated July 7, 1998). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 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 "FPL for approved supplements NDA 20-482/S-007 and S-008." Approval of this submission by FDA is not required before the labeling is used.

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

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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

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

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

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

Sincerely,

/S/ 9/28/98

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

cc:
Archival NDA 20-482
HFD-510/Div. Files
HFD-510/Jweber/EGalliers
HFD-510/MFossler/HYAhn/XYsern/SMoore/RSteigerwalt/GAras/TSahlroot/ENevius/
RMisbin/GTroendle
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - for drug discussed at advisory committee meeting.
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: JMW/August 28, 1998
Initialed by:MFossler 8/25/HYAhn 8/28/XYsern & Smoore 8/31/RSteigerwalt 8/31/GAras
9/1/ENevius 9/1/TSahlroot 8/31

final:JWeber/9/24/98 /S/ 9/24
filename: N20482.SAP

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20482/S007/S008

MEDICAL REVIEW(S)

SEP 28 1998

Diabetes89

NDA 20482/S007, S008
Bayer
Acarbose for Combined Use with Insulin or Metformin
Received by Team Leader 9/25/98
Review Written 9/28/98

TEAM LEADER'S REVIEW

Acarbose was approved in 1995 for monotherapy of type 2 diabetes, and for combined use of acarbose with sulfonylureas. These supplements contain data to support the use of acarbose in combination with insulin or metformin. The data show that when patients who were inadequately treated with near maximal doses of metformin had acarbose added to the regimen (study 95-020, 74 pbo and 73 acarbose pts, 25 mg for 4 weeks, 50 mg for another 8 weeks and optional increase to 100 mg for the remaining 12 weeks), HbA1c decreased 0.65% at 24 weeks, compared to randomly assigned placebo patients. As with monotherapy, adverse events in the acarbose patients were mostly gastrointestinal and did not result in irreversible or life-threatening injury.
A similar study (study 96-004) was conducted in patients inadequately treated with insulin. The insulin dose was held constant, and acarbose or placebo was administered. At 24 weeks the HbA1c was lower in the acarbose group by 0.63%. Safety remained acceptable, and safety update showed no change in the profile of events.
See Staticians review for supportive studies D87-009, 0626.

Recommendation: Supplements 007 and 008 Approvable

/S/

Gloria Troendle

NDA 20-482 ACARBOSE

Sponsor: BAYER

S-007 Use of Precose in patients with type 2 diabetes treated with diet plus insulin
- submitted September 29, 1997

S-008 Use of Precose in patients with type 2 diabetes treated with diet plus metformin
- submitted November 24, 1997

Revised Package Insert submitted February 1998

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Background:

Acarbose(Precose) was approved in late 1995 for treatment of type 2 diabetes mellitus both as monotherapy and in combination with sulfonylureas. The Sponsor had submitted amendments requesting approval for use in combination with metformin and in combination with insulin. However, approval of these indication was not granted.

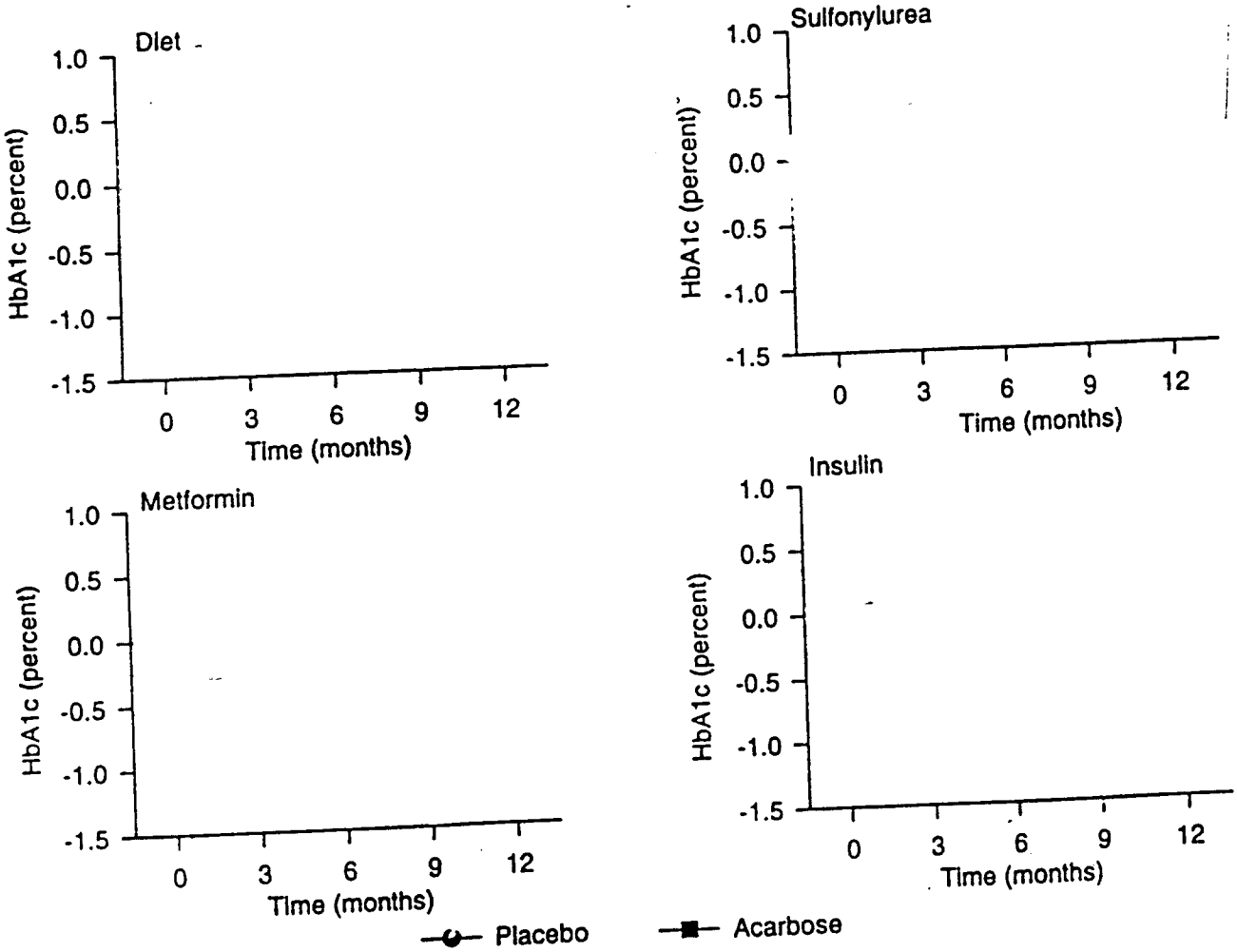
By way of background, it is helpful to refer to study 0626 of the original application, because this study is the only one in which efficacy data for all four indications are presented together. This was a 12 month study conducted in Canada. As shown in figure 1, acarbose had a consistent effect on reduction of hemoglobin A1c both as monotherapy and in combination with oral agents which persisted for 12 months. Starting mean HbA1c was about 6.7% for patients on diet alone, 7.8% for patients on insulin, 8.0% for patients on metformin and 7.7% for patients on insulin. The fall in HbA1c of 0.8% in patients on metformin was similar to the fall of 0.9% for patients on diet alone or sulfonylureas and was statistically significant (p=0.01). The metformin arm consisted of only 42 patients who completed the trial . This was felt to be an inadequate data base particularly since both acarbose and metformin cause gastrointestinal adverse events which could possibly be potentiated when the drugs are used in combination. It was also noted that there had been a recent report that acarbose decreased absorption of metformin in normal subjects. Furthermore, patients were not on the maximal dose of metformin. Therefore the addition of acarbose could not be said to have caused a reduction in HbA1c that could not also have been achieved by maximizing current therapy. For these reasons, approval of metformin-treated patients was denied. The reduction in HBA1c of 0.4% for insulin-treated patients was not statistically significant. Although this reduction in HbA1c was accompanied by a small reduction in insulin dose, the Division was not willing to accept these results as a positive study. Therefore approval of acarbose for insulin-treated patients was also not denied.

Following initial approval of acarbose as monotherapy or as an adjunct to sulfonylureas, the Sponsor was told they would need to provide additional studies to obtain the metformin and insulin indications. Each of these new studies is discussed in detail below. A brief review of previous studies is also provided. The additional studies provide no unexpected information about safety.

APPEARS THIS WAY
ON ORIGINAL

Study 626

Change from Baseline in HbA1c



APPEARS THIS WAY
ON ORIGINAL

FIGURE 1

ACARBOSE WITH METFORMIN

Study D95-020

This study was conducted in the United States to examine the effect of the use of acarbose in patients with type 2 diabetes who were inadequately controlled on near maximal doses of metformin (2000 or 2550 mg) two months or longer. Each arm consisted of 84 patients. Their mean age was 56 years and duration of diabetes for 7.5 years. Mean BMI was 32.3 kg/m2. 55% were male, 83% Caucasian, 7% African American and 7% Latino. Baseline parameters for the placebo patients were HbA1c of 8.17% and fasting plasma glucose (FPG) of 195 mg/dl. Among the acarbose patients starting HbA1c was 8.46% and FPG was 204 mg/dl. These differences were not statistically different. The initial starting dose of acarbose was 25 mg tid which was increased to 50 mg tid at week four. The dose was raised to 100 mg tid for patients whose one hour postprandial glucose exceeded 160 mg/dl but could be dropped back to 50 mg tid if the higher dose was not tolerated. By the end of 24 weeks, 85% of patients in the placebo arm were on 100 mg tid, compared to 78% of patients with the acarbose arm.

Efficacy:

74 patients in each arm completed the study. Among placebo patients with mean change in HbA1c was 0.08%. Among acarbose patients the mean change was -0.57% , giving a mean placebo-subtracted treatment effect of -0.65(SEM = 0.15). Intent- to-treat analysis gave a treatment effect o -0.71% at 24 weeks. A time course of the effect on HbA1c, shown in figure 2, demonstrates that the effect of acarbose is durable in that the difference between acarbose and placebo is, if anything, increasing at the end of the 24 week study. Furthermore, HbA1c remained nearly constant in patiens on placebo so that virtually all of the efficacy in patients on acarbose was reflected by a fall in baseline. As shown in table 1, acarbose improved all of the secondary measures of glycemic control. As expected, the improvement in postprandial glucose was greater than fasting glucose or 24 hour urinary glucose, but even these last two measures were also improved with acarbose with a p value of about 0.02. Plasma insulin levels were also lowered by acarbose, particularly at 60 minutes and 120 minutes after eating. There was a minimal.,if any, change on serum lipids. 120 minute postprandial triglyceride rose 1.00 mg/dl in placebo patients (starting value 223.6) but rose 0.90 mg/dl(starting value 230.4) in acarbose patients. Although significant with a p value of 0.014, this change is probably of no clinical importance. Fasting triglyceride, HDL and LDL cholesterol were unchanged at about 180mg/dl, 117 mg/dl, and 44 mg/dl respectively .

Safety:

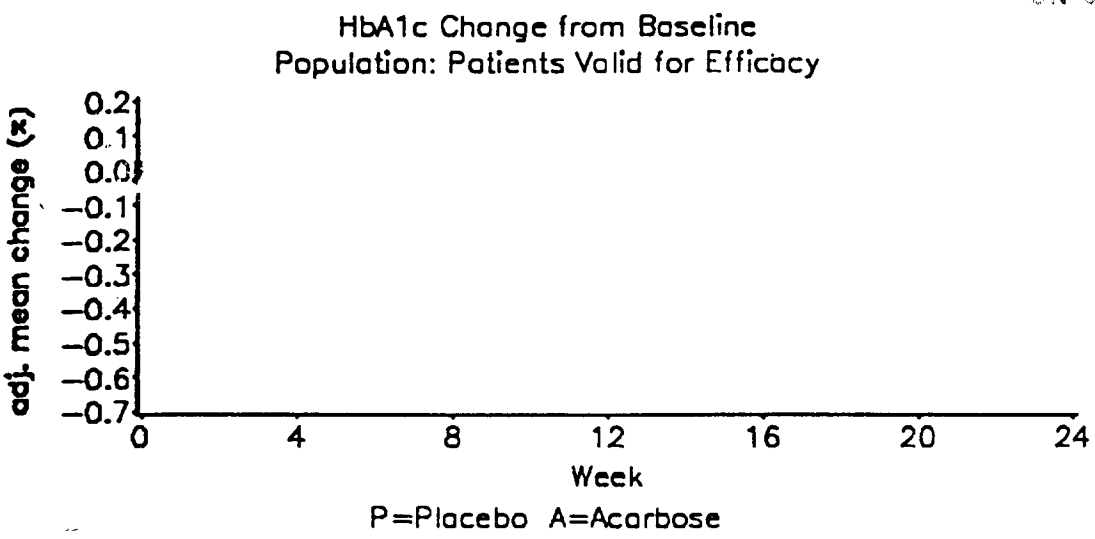
10 patients discontinued because of an adverse event in the acarbose arm compared to 3 patients in the placebo arm. Gastrointestinal complaints were the cause of discontinuation in 7 patients on acarbose and 2 on placebo. The other causes were unrelated to treatment. 1 patient in each arm dropped out because of lack of efficacy. There were no deaths.

Gastrointestinal complaints were reported more frequently ($p<0.0005$) in acarbose patients (56%) than in placebo patients (29%). Flatulence was reported more frequently ($p<0.0005$) in acarbose patients (31%) than in placebo patients (5%). There were trends for more diarrhea (17% vs 11%) and abdominal pain (8% vs 6%) in acarbose patients than in placebo patients but the differences were not statistically significant. The rates of gastrointestinal events reported in this study are, if anything, lower than what has been reported in other acarbose studies. This seems to suggest the possibility that patients already on metformin are accustomed to gastrointestinal symptoms so that the addition of acarbose does not matter. Alternatively, tolerability to metformin preselects patients who will also be tolerant to acarbose. In any event, the Division's concern that the addition of acarbose to metformin might lead to an unacceptably high rate of gastrointestinal complaints has not been borne out.

Pharmacokinetics:

Metformin blood levels were measured before and 2 hours after dosing with 1000 mg of metformin. There was a mean 12% decrease in both basal and post-dose metformin blood levels in patients on acarbose compared to placebo at 24 weeks as shown below. Smaller differences were seen earlier. The 90% confidence interval for the ratio of the basal level is 0.73-1.07 and for the ratio of the 2 hour levels is 0.75 - 1.01

	Metformin blood levels at 24 weeks, ng/ml	
	before dose	2 hr post 1000 mg dose
placebo	514	1467
acarbose	455	1283



The results were similar in the intent-to-treat population: The placebo-subtracted difference at double-blind endpoint was -0.71% (SE=0.13%).

For the secondary efficacy variables, the adjusted mean changes at the double-blind endpoint are summarized below for the population of patients valid for efficacy, for all variables except triglycerides and normalized urinary albumin excretion. For these, the summary statistics presented are geometric adjusted means of the ratio of the endpoint value to the baseline value.

Change from Baseline in Secondary Efficacy Variables
Population: Patients Valid for Efficacy

	Adjusted Mean Changes		
	Placebo	Acarbose	P-value
Fasting plasma glucose (mg/dL)	1.83 A	-12.70	0.0213
60-min. plasma glucose (mg/dL)	3.33 A	-30.99	0.0001
90-min. plasma glucose (mg/dL)	5.90 A	-33.30	0.0001
120-min. plasma glucose (mg/dL)	5.52 A	-36.50	0.0001
Plasma glucose total AUC (mg*min/dL)	482.0 A	-3259.9	0.0001
Fasting serum insulin (uIU/mL)	2.03 A	-1.93	0.0291
60-min. serum insulin (uIU/mL)	0.84	-5.59	0.0657
90-min. serum insulin (uIU/mL)	2.80 A	-5.78	0.0167
120-min. serum insulin (uIU/mL)	-0.28 A	-10.35	0.0043
Serum insulin total AUC (uIU*min/mL)	162.5 A	-601.6	0.0144
Fasting triglycerides*	1.02	0.94	0.0856
60-min. triglycerides*	0.97	0.97	0.9225
90-min. triglycerides*	1.00	0.94	0.1911
120-min. triglycerides*	1.00 A	0.90	0.0177
Triglycerides total AUC*	1.00	0.95	0.2492
Total cholesterol (mg/dL)	6.53	5.79	0.8299
HDL cholesterol (mg/dL)	1.45	0.71	0.4383
LDL cholesterol (mg/dL)	4.21	8.22	0.1694
Normalized urinary albumin*	1.13	1.12	0.9253
Normalized urinary glucose (g/day)	2.80 A	-7.57	0.0178

* geometric adjusted mean of the ratio of the endpoint value to the baseline value

A: Significantly different from acarbose

ACARBOSE WITH INSULIN

As discussed above, study 026 demonstrated a fall in HBA1c of 0.4% which was not statistically significant. Study 87-009 was a 24 week study previously done in Europe with 107 patients in the acarbose arm and 110 patients in the insulin +placebo arm. HbA1c feel 0.17% in the placebo group and 0.57% in the acarbose group. The acarbose treatment effect was the same -.4% as in study 026, but here it was highly significant(p=0001). There was also a net 8% fall in insulin dose(p=0015) in the acarbose group with no difference in the number of hypoglycemia episodes.

Study 96/004

This double blind placebo-controlled study was done at the request of FDA to constitute a pivotal trial for the treatment of NIDDM with acarbose in combination with insulin. Inclusion criteria were type2 diabetes on a stable insulin for two months with HbA1c of Following a 2 week run-in period, patients were treated with acarbose 25 mg tid for four weeks followed by 50 mg tid for 8 weeks. The dose could then be raised to 100 mg tid for the remainder of the 24 week active treatment period. Inorder to isolate the effects of acarbose from those due to changes in insulin regimen, patients were required to maintain a constant total insulin dose for the entire duration of the study. The only exception was for insulin coverage provided during a hospitalization for a cause not solely related to diabetes control (such as insulin coverage during hospitalization for an acute myocardial infarction). These patients could receive short-term in-patients increases in their insulin dose according to the following rules:

no more than four consecutive days per treatment episode
no more than 2 such episodes per 56 days
no more than 2 such episodes during the entire study

Data from patients who do not meet these rules were excluded from the analysis done by the Sponsor. However, they are included in this review and in the statistical reviewer's report but are analyzed separately as described later.

Rates of premature discontinuation are as follows:

	Placebo		Acarbose	
	n=97	%	n=98	%
any reason	23	24	34	35
adverse event	6	6	19	19
lack of efficacy	3	3	1	1
protocol violation	7	7	4	4

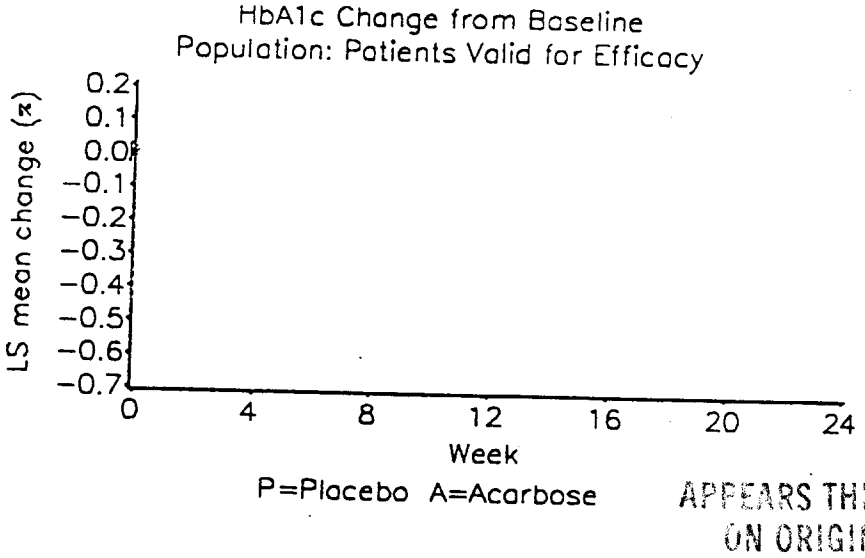
Removal of patients due to adverse events, mostly gastrointestinal, was more frequent in the acarbose group (p=0.009). Demographics were the same in both groups. Patients had a mean age of 61 years, and mean duration of diabetes of 12.4 years. They were 55% male and 87% Caucasian. Placebo patients took a mean insulin dose of 60.2 units compared to 62.0 units in the acarbose patients. Mean HbA1c at baseline was 8.69% for placebo patients and 8.77% for acarbose patients. At the end of the 24 week active treatment period 89% of placebo patients and 80% of the acarbose patients were on the 100 mg tid dose. As shown on the next pages(taken directly from the NDA) the placebo-subtracted change from baseline in HbA1c was -0.69% in the valid for efficacy population and -0.63% in the intent-to treat population. While there was little change in HbA1c over the 24 week study, the fall in acarbose patients was continuing even at the end of the study. Using the criteria of a fall in HbA1c of at least 0.7% , the response rate in acarbose patients was 42% compared to 23% for placebo patients.(p=0.01). Postprandial glucose, urinary glucose and triglycerides were also significantly reduced by acarbose. Although not statistically significant, there was a small reduction in fasting glucose.

HbA_1c Results (%) at Double-Blind Endpoint

Treatment	Change from Baseline N	LS Mean	Standard Error	Placebo-Subtracted Change from Baseline (Standard Error)
Placebo	73	0.11 A	0.12	
Acarbose	72	-0.58	0.12	-0.69 (0.17)

A: Significantly different from acarbose

Furthermore, at each visit, acarbose was superior to placebo ($p<=0.0018$). The results at the visits are plotted below.



The results were similar in the intent-to-treat population. Acarbose was significantly superior to placebo at every visit and at double-blind endpoint. The placebo-subtracted difference at double-blind endpoint was -0.63% (SE=0.14%).

Change from Baseline in Secondary Efficacy Variables

	LS Mean Changes		
	Placebo	Acarbose	P-value
Fasting plasma glucose (mg/dL)	8.87	-2.84	0.4221
60-min. plasma glucose (mg/dL)	8.03 A	-27.99	0.0178
90-min. plasma glucose (mg/dL)	5.68 A	-49.95	0.0004
120-min. plasma glucose (mg/dL)	6.51 A	-55.32	0.0001
Plasma glucose AUC (mg*min/dL)	859.69 A	-3964.2	0.0074
Fasting triglycerides*	0.99	0.90	0.0546
60-min. triglycerides*	0.99	0.90	0.0617
90-min. triglycerides*	0.96 A	0.83	0.0050
120-min. triglycerides*	0.96 A	0.82	0.0133
Triglycerides AUC*	0.97 A	0.86	0.0223
Total cholesterol (mg/dL)	-2.98	-0.43	0.4460
HDL cholesterol (mg/dL)	-0.44	-1.24	0.4341
LDL cholesterol (mg/dL)	-2.43 A	6.83	0.0018
Normalized urinary albumin*	1.23	1.13	0.5113
Normalized urinary glucose (g/day)	6.21 A	-5.41	0.0074

* geometric LS mean of the ratio of the endpoint value to the baseline value

A: Significantly different from acarbose

Among placebo patients there were 19 whose efficacy data were excluded because of change in insulin dose. There were 18 such acarbose-treated patients. Although not tabulated in the original submission, the Sponsor was asked to submit HbA1c data on these patients separately. In analyzing these data, I scored a patient as "better" if HbA1c fell by >0.5% accompanied by a reduction in insulin dose. I scored patients as "worse" if HbA1c rose by >0.5% accompanied by an increase in insulin dose. Patients were considered neither better nor worse if HbA1c changed by 0.5% or less, or if the change in HbA1c and change in insulin dose were in opposite directs.
Results are as follows:

			PLACEBO		ACARBOSE
Better,	n=	2	(11%)	8	(44%)
Worse,	n=	3	(16%)	3	(17%)
Total,	n=	19	(100%)	18	(100%)

These results shows that exclusion of patients with changes in insulin dose from the primary efficacy analysis does not artifactually bias the results. Even patients whose insulin dose changes showed a net improvement on acarbose vs placebo(p=0.026)

Reports of symptoms suggestive of hypoglycemia occurred in 30% of acarbose patients compared to 23% of placebo patients. The difference was not statistically significant and could have been accounted for by lower HbA1c in the acarbose patients. As expected, more acarbose patients (77%) had gastrointestinal complaints, primarily flatulence, than placebo patients (41%). A curious finding was a statistically significant difference in adverse events related to the nervous system , 24% of placebo patients compared to 13% of acarbose patients. This was related to a few cases of depression, paresthesias. Or hypesthesias in the placebo group. Having not been reported before, this finding was felt to be spurious.

There were no deaths in the study.

APPEARS THIS WAY
ON ORIGINAL

SAFETY REVIEW:

The two new studies in the supplements do not provide any unexpected information. Gastrointestinal complaints continue to be the major problem related to treatment with acarbose. Addition of patents from the new studies will change the label only slightly:

	Current label		New Label	
	Precose	Placebo	Precose	Placebo
n=	1075	818	1255	919
abdominal pain	21%	9%	19%	9%
diarrhea	33%	12%	31%	12%
flatulence	77%	32%	74%	29%

There was no increase in transaminase elevation in acarbose vs placebo patients in the two new studies. This was also the case in the previous placebo-controlled studies for patients whose acarbose dose did not exceed 100 mg tid., the maximum recommended dose. Spontaneous reports of two deaths in Japan due to fulminate hepatitis from a marketing experience of over three million patients worldwide had been noted previously.

LABELING ISSUES

Comments relating to submission of February 13, 1998 with revised labeling for the two supplements S007(acarbose plus insulin) and S008 (acarbose plus metformin).

PK - Both peak and steady state metformin levels were reduced slightly in patients on acarbose. This should be included in the label. I do not understand the justification for saying that the total amount of metformin absorbed was equivalent.

Table 2 is unacceptable as revised. The original table 2 showed baseline values and mean changes from baseline. This data needs to be retained. The legend to table 2 is misleading. The reduction in dose of background medication was not considered a measure of efficacy on which approval was based. Some of the data in the table is unnecessary, such as the results at 200 mg tid with SFU. The information in the section "clinical experience in NIDDM patients receiving insulin" should be retained.

I would suggest the following:

Figure of 12 month time course of placebo subtracted HbA1c from study 0626 for all classes of patients.

Replace table 2 with a table showing results from studies in which the dose of background therapy was kept constant. This would include the two recent USA studies (95-020 metformin and 96-004 insulin) and the SFU data from the previous Canadian study (0626) . The results for monotherapy from 0626 should also be shown for comparison. This table should follow the same format as table 2 in the original label and should show baseline and change from baseline for HbA1c. To be consistent and avoid confusion I would show the 6 month data from 0626. The 12 month data is already in the figure. Fasting, and 1 hr pp glucose could also be added

SUMMARY:

There are two placebo controlled trials which demonstrate the efficacy of acarbose in combination with metformin. The reduction in HbA1c relative to placebo after six months was 0.8% in the Canadian study reported originally and 0.65% in the more recent US study. There was no increase in gastrointestinal events reported by patients using acarbose in combination with metformin than by patients using acarbose monotherapy or acarbose in combination with sulfonylureas. There are three placebo-controlled studies which support the efficacy of acarbose in combination with insulin. For patients in whom the insulin dose remained constant, the reduction in HbA1c relative to placebo in study 96/004 was 0.69% virtually the same as the reduction seen with metformin in study D95-020. Taken together with results of other trials, it appears that the intrinsic efficacy of 50 -100 mg tid acarbose is about 0.7% when used either by itself, or in combination with fixed doses of other oral agents or with a fixed dose of insulin.

Variability in the insulin dose can partially offset the effects of acarbose. The net effect in the two studies where the insulin dose was allowed to vary was a reduction in HbA1c of 0.4% .This was statistically significant in one study only. Therefore DMEDP did not accept these two studies as having established the efficacy of acarbose in insulin-treated patients and insisted on additional data. The new study 96/004 shows that the efficacy of acarbose in insulin-treated patients is about the same as in other classes of patients. The apparent discrepancy among these studies is related to the fact that patients were sometimes allowed to adjust their doses of insulin. I might not have been willing to accept the results of 96/004 as the sole proof of efficacy because requiring inadequately controlled patients to maintain a constant insulin dose is contrary to standard practice. However, when viewed in light of the two other studies, it is clear that the efficacy of acarbose persists even if patients adjust their dose of insulin.

RECOMMENDATION:

Taken together with previous studies, the results of the new studies submitted in these supplements show that acarbose is safe and effective for treatment of type 2 diabetes when used on a background of metformin plus diet or insulin plus diet. The revised label is misleading and needs to be changed along the lines of the suggestions made earlier. Assuming these changes are made, I recommend that the supplements be approved.

/S/

Robert I Misbin MD
DMEDP/HFD 510
Medical Officer
May 29, 1998

/S/
9.25.98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20482/S007/S008

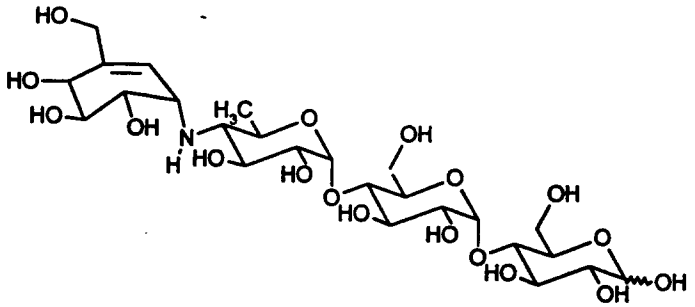
CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. ORGANIZATION CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	**2. NDA #** 20-482 Original NDA approved: 06-SEP-1995
3. NAME AND ADDRESS OF APPLICANT Bayer Corporation Pharmaceutical Division 400 Morgan Lane West Haven, CT 06516-4175 Phone (203) 812-3051	**4. SUPPLEMENT(S)** SEI-007 Doc.29-SEP-1997 Rec.30-SEP-1997 SEI-008 Doc.24-NOV-1997 Rec.25-NOV-1997
	5. Name of the Drug Precose
	6. Nonproprietary Name Acarbose
7. SUPPLEMENTS PROVIDES the documentation to demonstrate the safety and efficacy for the use of acarbose in: (1) type 2 diabetes treated with diet plus insulin (SEI-007), and (2) type 2 diabetes treated with diet plus metformin (SEI-008).	**8. AMENDMENT** Doc. 13-FEB-1998 Rec. 17-FEB-1998 for SEI-007 and SEI-008

9. PHARMACOLOGICAL CATEGORY Hypoglycemic agent. Inhibitor (α-glucosidase).	**10. HOW DISPENSED** Rx	**11. RELATED** -N. A. -
12. DOSAGE FORM Tablet	**13. POTENCY** 25, 50 and 100 mg	

14. CHEMICAL NAME AND STRUCTURE



Acarbose (Bayer's code name Bay g5421)
$C_{25}H_{43}NO_{19}$
F.W. = 645.62
CAS 56180-94-0

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

15. COMMENTS Supplements 7 and 8 provide for the use of acarbose for two new therapeutical applications. Supplement SEI-007 provides the documentation to demonstrate the safety and efficacy for the use of acarbose for type 2 diabetes treated with diet plus insulin. Supplement SEI-008 provides for the use of acarbose for type 2 diabetes treated with diet plus metformin. The drug product will not be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect.

According to 21CFR §25.24(c)(2) requirements for **categorical exclusion of Environmental Assessment are met**

16. CONCLUSIONS AND RECOMMENDATIONS Adequate. **These supplements may be approved from the chemistry viewpoint.**

17. REVIEWER NAME (AND SIGNATURE) **DATE COMPLETED** 24-FEB-1998

Xavier Ysern, PhD /S/

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/S/
2/26/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20482/S007/S008

PHARMACOLOGY REVIEW(S)

NDA 20-482/S007

Review Completed: September 24, 1998

Sponsor: Bayer Corporation Pharmaceutical Division; West Haven, CT 06516

PHARMACOLOGY REVIEW OF NDA SUPPLEMENT

Supplement to NDA 20-482 #007

DRUG: **Precose® (Acarbose, BAYg5421)** (in conjunction with metformin)

CATEGORY: **Antidiabetic.** Precose® is an oral alpha-glucosidase inhibitor for use in management of type 2 diabetes mellitus.

INDICATION: This supplement provides for use in combination with metformin in the lowering of blood glucose as an adjunct to diet.

PHARMACOLOGY COMMENTS: There were no preclinical data submitted under supplement #007. Therefore, no pharmacology review is necessary for this supplement. Labeling comments are addressed in the review for supplement #008.

/S/

Ronald W. Steigerwalt, Ph.D.

cc: NDA Arch
HFD510
HFD510/Steigerwalt/Weber
Recommendation code: AP

NDA 20-482/S008 **Review Completed: March 16, 1998**

Sponsor: Bayer Corporation Pharmaceutical Division; West Haven, CT 06516

Date Submitted: November 24, 1997

Date Received: November 25, 1997

DRUG: Precose (Acarbose)

CATEGORY: Antidiabetic

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V.	Recommendation (AP)	10
VI.	**To Be Communicated To Sponsor**	**10**

/S/

Ronald W. Steigerwalt, Ph.D.

cc: NDA Arch
HFD510
HFD510/Steigerwalt/Johnston
Recommendation code: AP

NDA 20-482/S008 **Review Completed: March 16, 1998**

Sponsor: Bayer Corporation Pharmaceutical Division; West Haven, CT 06516

Date Submitted: November 24, 1997 **Date Received: November 25, 1997**

PHARMACOLOGY REVIEW OF NDA SUPPLEMENT
Supplement to NDA 20-482 #008 (November 25,1997)

DRUG: Precose® (Acarbose, BAYg5421) (in conjunction with metformin)

CATEGORY: Antidiabetic. Precose® is an oral alpha-glucosidase inhibitor for use in management of type 2 diabetes mellitus.

INDICATION: This supplement provides for use in combination with metformin in the lowering of blood glucose as an adjunct to diet.

INTRODUCTION

Precose® (Acarbose tablets) is an oral competitive, reversible alpha-glucosidase inhibitor for use in management of type 2 diabetes mellitus. It is currently approved for monotherapy and in conjunction with sulfonylureas. Precose® is currently under consideration for combination use with insulin or metformin (supplements 007 and 008). Chemically, it is an oligosaccharide obtained from fermentation *of Actinoplanes utahensis.* It is available as 25, 50 and 100 mg tablets for oral use. Recommended initial dose of Precose® is 25 mg given orally t.i.d. with the start of each main meal. Maintenance dose is up to 100 mg t.i.d., however, the labeling recommends that only patients with body weight >60 kg should receive doses above 50 mg t.i.d.. Since the mechanism of action is different, the sponsor claims that glycemic control is additive to sulfonylureas, insulin and metformin and could be used in combination for enhanced glycemic control. The purpose of the studies submitted in this supplement was to examine the potential for interaction of Acarbose with these oral hypoglycemic agents.

Precose® is largely unabsorbed. Approximately 51% of an oral dose is eliminated in the feces. Of the active drug that is absorbed, excretion appears to be primarily renal. Since the mode of action is non-systemic, the low absorption is desirable.

REVIEW OF STUDY PH23643:
BAY g5421/ SUBACUTE PHARMACODYNAMIC INTERACTION STUDY IN RATS OF ACARBOSE WITH METFORMIN, GLYBENCLAMIDE AND CHLORPROPAMIDE

NOTE: Performed by sponsor
Study date January 17, 1995. Signed QA/GLP statement provided (dated December 21, 1994.) Acarbose batch #266676H purity 95.5%. Metformin lot # 018F0672
(98.8% purity, Glybenclamide lot #091H3449
99.9% purity, Chlorpropamide lot # 031H0722 99.6% purity.

PURPOSE: To determine any pharmacodynamic or toxicologic interaction of Acarbose at the highest clinical level (mg/kg clinical dose) as well at a 10-fold higher dose compared with

combination of three oral antidiabetics currently on the market which could be potentially used in combination with Acarbose. The doses of oral hypoglycemic drugs was approximately 2-3 times the clinical recommended dose based on mg/m^2 comparisons.

EXPERIMENTAL DESIGN: Treatment during this study was for 4 weeks. 10 Wistar rats (SPF Hsd/Win: WU)/sex/group were administered Bay g 5421 at dietary concentrations of 0, 150 and 1500 ppm (corresponding to 11 or 146 mg/kg body weight/day) with or without combination treatment (combination treatments were administered by gavage as outlined below). Dosing groups were as illustrated in Table 1 (males and females are combined in this table, sponsor labeled male and female groups separately for a total of 24 groups). Vehicle for gavage administration: 0.5% Aqueous carboxymethyl cellulose.

Table 1: Dose groups for Study PH23643

GROUP #	DOSE			
	Acarbose (dietary) (mg/kg)	Metformin (gavage) (mg/kg)	Glybenclamide (gavage) (mg/kg)	Chlorpropamide (gavage) (mg/kg)
1	0			
2	11			
3	146			
4	0	175 bid		
5	0		3	
6	0			60
7	11	175 bid		
8	146	175 bid		
9	11		3	
10	146		3	
11	11			60
12	146			60

Rationale for dose selection: Sponsor claimed that doses of Acarbose were selected on the basis of a 30 month carcinogenicity study in Wistar rats. However, the specific basis for selection is not provided. On a mg/m^2 basis, the acarbose doses represent a dose slightly lower than maximal clinically recommended dose (using 50 mg tid in a 60 kg human as basis for comparison) and a dose approximately 10-fold higher. The doses of the other antidiabetic drugs were based on data from pharmacology and pharmacokinetics in humans and rats. Based on a mg/m^2 comparison, the combination drugs were dosed at approximately the recommended clinical exposure.

Laboratory tests on blood were performed during week 3-4 in all animals. Samples for the profile of glucose, lactate and insulin were obtained from all animals on days 15, 16 and 17 at 2, 4, 6 and 12 h after the afternoon gavage administration.

RESULTS

OBSERVED EFFECTS: The high dose of Acarbose increased fecal excretion in all males (irrespective of combination treatment) and some females after combined treatment.

MORTALITY: No test agent related effects. One male rat (LD Acarbose/metformin treatment - group 7) died on day 12. One female rat (metformin alone - group 4) died on day 28. It was determined that these deaths were the result of gavage accidents.

BODY WEIGHT: Combination of high dose Acarbose and metformin (group 8) resulted in statistically significantly lower mean group body weights in males compared to untreated controls. This was evident by week 1 and reached a maximum of 11% decreased body weight at week 2. High dose Acarbose and glybenclamide (group 10) also had statistically significantly lower body weights (7%) compared to controls. The effect with glybenclamide combination (group 10) was slight and apparently transient compared to the high dose Acarbose alone group (group 3). Other mean values were up to 5% decreased, but were not statistically significant. Females appeared unaffected in any group.

FOOD CONSUMPTION: Feed intake was increased (in males, in females) in rats treated with the HD of Acarbose irrespective of combination therapy. Water intake was also increased in HD Acarbose treated animals regardless of combination therapy. Metformin alone also increased water consumption.

VITAL SIGNS: No data.

OPHTHALMIC EXAMINATION: No data.

HEMATOLOGY: No treatment-related effects.

COAGULATION: No data.

BONE MARROW: No data.

BLOOD CHEMISTRY: Parameters Measured: ASAT (GOT), ALAT (GPT), AP, GLDH, Triglycerides, HST Urea.
MALES: Increased ASAT, AP and GLDH were noted in the HD Acarbose males. In combination with glybenclamide, findings were similar. In combination with metformin, ASAT and GLDH were increased to an extent similar to, though slightly higher than, Acarbose alone. There were no statistically significant differences noted with chlorpropamide alone or in combination with Acarbose, although there were some elevations, particularly with AP and GLDH in individual animals. Most elevations were <50% with Acarbose alone or incombination, but the increases in GLDH were up to 2.5 times control values with HD Acarbose alone and in combination with metformin, indicating that although this was increased, there was no additive effect of the combination.
FEMALES: Increased ASAT, ALAT, AP AND GLDH were noted in animals treated with the HD Acarbose alone or in combination with other drugs. There was no apparent additive effect of combinations. Increases were generally smaller than those noted for males.

Triglycerides were significantly decreased in HD Acarbose male rats. However, there was no additional effect of combination treatment. This did not occur in females.

GLUCOSE:
LD Acarbose: no effect.
HD Acarbose: tendency to decreased glucose in males.

Metformin: transient tendency for decreased glucose during the afternoon administration in males. In females, tendency to lower glucose levels at 2, 4 and 6 h (significant at 4 h) .
HD Acarbose + metformin: no enhancement of Acarbose alone in males. In females, the combination of either dose of Acarbose and metformin resulted in a statistically significant decrease in glucose at 2 h, but not later.

Glybenclamide: Significant reduction in glucose irrespective of cotreatment. Most consistent effect was at 2 h where there appeared to be an increased effect of the combined therapy.

Chlorpropamide: Strongest glucose lowering effect at 2 h with no additive effect of Acarbose in either sex. No effect was seen in males at 4 or 6 h although there were increased glucose levels in all groups at 12 h. In females, there was a slight effect at 4 h which was not evident at 6 h.

LACTATE: Interpretation was confounded by relatively high interindividual variation. Significant increase was noted in females at 4 h receiving metformin alone. It is concluded that none of the test agents induced lactic acidosis alone or in combination with Acarbose.

INSULIN: Interpretation was confounded by high interindividual variation. Insulin concentrations in serum were consistently lower in male rats receiving HD Acarbose with or without cotreatment. There did not seem to be an additive or potentiating effect of cotreatment.

URINALYSIS: No data.

ORGAN WEIGHTS: No treatment-related effects with individual test agents or in combination.

GROSS PATHOLOGY: Cecal enlargement was noted in most animals treated with HD Acarbose irrespective of cotreatment. There were no other treatment-related findings or indication of an effect with cotreatment.

HISTOPATHOLOGY: In a few animals, isolated dilated crypts or very slight round cell infiltrates were observed without dose correlation. However, there were no clear histopathological correlates with the cecal enlargement noted grossly. Elongated pancreatic islets appeared to be slightly more frequent in males than in females, but there was no indication of increased incidence or severity of elongated islets in any treatment groups when compared to controls. One male treated with glybenclamide had a focal islet cell hyperplasia which could not be ruled out as an induced finding. However, this did not appear to be increased with combination treatment.

Males also exhibited an increase in basophilic cortical tubules of the kidney, but again, this did not change in incidence or severity with dosing.

There was a decreased incidence and grade of plaque-like hepatocellular cytoplasm in the HD Acarbose animals irrespective of cotreatment. This was interpreted as a morphological correlate of decreased glycogen content and did not appear to be affected by combination treatment.

SUMMARY

Wistar rats were treated with Acarbose in concentrations of 0, 150 or 1500 ppm in diet with or without additional daily treatment with 2 X 175 mg metformin/kg, 3 mg glybenclamide/kg or 60 mg chlorpropamide/kg by gavage for 4 weeks. There were no toxicological interactions with any of the 3 antidiabetics at either dietary concentration of Acarbose. Additive effects on glucose levels were noted with combinations of acarbose with metformin (female rats) or glybenclamide, but these were transient, being evident at 2 h after dosing, but not at later timepoints. Insulin levels were lowered by acarbose alone, but there did not appear to be an additive effect with combination treatment. It is notable that there was a significant increase in lactate in females at 4 h receiving metformin alone, but there did not appear to be any additive effect with acarbose. It did not appear that combination treatment would exacerbate lactic acidosis.

Blood chemistry changes were suggested to be due to an increase in gluconeogenesis. In the first weeks of treatment with high doses of Acarbose, a complete malabsorption of glucose occurs. This shifts metabolism to the utilization of amino acids as precursors to new glucose production. The sponsor suggests that this shift in metabolism is responsible for the increased synthesis of enzymes involved in amino acid-glucose metabolism (specifically, ASAT, ALAT and GLDH, which were the enzymes induced in this study).

REVIEW OF STUDY PH23746: PLASMA CONCENTRATIONS OF CHLORPROPAMIDE, GLYBENCLAMIDE AND METFORMIN IN MALE AND FEMALE WISTAR RATS WITH AND WITHOUT CONCOMITANT ACARBOSE FEEDING

NOTE: Study performed by sponsor at Bayer Corporation, Wuppertal, Germany. Study dates range from April 1994-June 1994 (each combination drug was studied separately). Study report dated February 6, 1995. Acarbose batch #266676H purity 95.5%. Metformin lot #018F0672 Glybenclamide lot #091H3449
Chlorpropamide lot #031H0772

PURPOSE: To determine any pharmacokinetic interaction of Acarbose compared with combination of three oral antidiabetics currently on the market which could be potentially used in combination with Acarbose. The aim was to deliver similar exposure to the oral hypoglycemics as human therapeutic doses while using a relatively high dose of Acarbose compared to human therapeutic levels.

EXPERIMENTAL DESIGN: 5 Wistar rats/sex/group were dosed with 175 mg/kg metformin (bid) or 60 mg/kg chlorpropamide or 5 mg/kg glybenclamide (qd) for 10 days with or without the dietary administration of Acarbose at 1500 ppm (146 mg/kg). Serial blood samples were taken from the retroorbital vein at 2, 5, 8 and 24 h after administration of chlorpropamide and glybenclamide and 2, 5,8 and 16 h after the first administration of metformin on day 7. The geometric mean and standard deviation of individual plasma concentrations was calculated. Note: half-lives were calculated on the base of only 2-4 data points, therefore, this is only a very rough estimate. Groups in this study were as listed below:

Table 2: Dose groups for Study PH23746

GROUP #	DOSE			
	Acarbose (dietary) (mg/kg)	Metformin (gavage) (mg/kg)	Glybenclamide (gavage) (mg/kg)	Chlorpropamide (gavage) (mg/kg)
1	0			
2	146			
3	0	175 bid		
4	0		3	
5	0			60
6	146	175 bid		
7	146		3	
8	146			60

RESULTS

CHLORPROPAMIDE (60 mg/kg): T_{max} was reached at 2h and was not affected by sex or feeding with Acarbose (differences <10%).
$AUC_{(0-24)}$ was 2508 mg•h/l without Acarbose and 2602 mg•h/l with Acarbose. In males, $AUC_{(0-24)}$ was 2839 mg•h/l without Acarbose and 2031 mg•h/l (about 30% lower) with Acarbose feeding. Interindividual variation was relatively low with geometric standard deviations below 1.37. AUC exposures to chlorpropamide in this study were similar administration of 250 mg chlorpropamide in humans (1723 mg•h/l in 18 male volunteers (C_{max} 30.3 mg/ml) and 1875 mg•h/l in 9 diabetic patients).

GLYBENCLAMIDE (5 mg/kg): T_{max} was reached 2-7 h after administration. In females mean C_{max} was 488 µg/l without Acarbose and 26% lower (361µg/l) in the Acarbose group. In males C_{max} was 116 µg/l (ie., clearly lower than females) without Acarbose and reduced by 29% with Acarbose (82.1 µg/l). This indicates first, a sex-specific difference of glybenclamide PK in rats and second, that glybenclamide exposure was decreased in both sexes when Acarbose was present in the diet. Results with AUC were similar: In females, mean $AUC_{(0-24)}$ was 9809 µg•h/l without Acarbose and 35% lower with feeding (6364 µg•h/l). In males, mean $AUC_{(0-24)}$ was 1004 µg•h/l (nearly 10 fold lower compared to females). Acarbose feeding decreased $AUC_{(0-24)}$ in male rats by 48% to 552 µg•h/l. AUC exposures to glybenclamide in this study were similar (slightly lower in males, slightly higher in female rats) compared to humans dosed with 5 mg glybenclamide Sex differences in rats were attributed to a higher P450 activity in male rat liver.

METFORMIN (175 mg/kg, bid):T_{max} was reached by 2 h after first administration on day 7 with no obvious sex differences. Without Acarbose, C_{max} was 7.81 mg/l in females and 9.48 in males. $AUC_{(0-16h)}$ were 35.4 and 38.4 mg•h/l, respectively. With Acarbose feeding, C_{max} declined by 32% (5.28 mg/l) in females and by 12% (8.38 mg/l) in males. $AUC_{(0-16)}$ also declined by 22% (27.6 in females and was negligibly in males (7%) There was high variability noted, particularly in females with geometric standard deviations of 1.7 to 2.7. Compared to human therapeutic doses: C_{max} after 1.0g metformin = 3.25 mg/l and $AUC_{(0-24)}$ of 19.8 mg•h/l. The rat exposure was approximately 2-fold higher than therapeutic doses in humans.

SUMMARY

The dose of Acarbose used was associated with carbohydrate malabsorption in rats with increased food uptake and fecal excretion. With all three combination oral hypoglycemic agents, overall exposure was moderately influenced probably by reduced absorption due to decreased gastrointestinal transit time by Acarbose.

Table 3: Summary Table of Plasma Concentrations and AUC After Administration of Oral Hypoglycemics With and Without Dietary Acarbose

Sex→	MALE		FEMALE	
Acarbose→	+ ACARBOSE	- ACARBOSE	+ ACARBOSE	- ACARBOSE
CHLORPROPAMIDE				
AUC (mg•h/l)	2031	2839	2602	2508
C_{max} (mg/l)	243	261	273	255
GLYBENCLAMIDE				
AUC µg•h/l	522	1004	6364	9809
C_{max} (µg/l)	82.1	116	361	488
METFORMIN				
AUC (mg•h/l)	35.7	38.4	27.6	35.4
C_{max} (mg/l)	8.38	9.48	5.28	7.81

OVERALL SUMMARY

Wistar rats were treated with Acarbose in concentrations of 0, 150 or 1500 ppm in diet with or without additional daily treatment with 2 X 175 mg metformin/kg, 3 mg glybenclamide/kg or 60 mg chlorpropamide/kg by gavage for 4 weeks. There were no obvious toxicological interactions with any of the 3 antidiabetics at either dietary concentration of Acarbose. Most observations (e.g., decreased body weights, increased food consumption, increased ASAT, AP and GLDH, cecal enlargement), appeared to be related to the high dose effects of Acarbose. There were no apparent additive effects of the combination therapies. Measurements of glucose suggested that while the individual agents alone had at least a tendency to decrease glucose levels, there did not appear to be a strong additive effect in the combination therapy. There was, however, a statistically significant decrease in glucose at the 2 h measurement with the combined treatment of metformin and Acarbose. There was a suggestion of a similar effect with glybenclamide, but there was no apparent combined effect with chlorpropamide. Measurements of lactate and insulin were confounded by high interindividual variation. However, particularly significant for the combination with metformin which induced an increase in lactate, there was no apparent induction of lactic acidosis with Acarbose alone or in combination with Metformin.

Blood chemistry changes were suggested to be due to an increase in gluconeogenesis. In the first weeks of treatment with high doses of Acarbose, a complete malabsorption of glucose occurs. This shifts metabolism to the utilization of amino acids as precursors to new glucose production. The sponsor suggests that this shift in metabolism is responsible for the increased synthesis of enzymes involved in amino acid-glucose metabolism (specifically, ASAT, ALAT and GLDH, which were the enzymes induced in this study). In combination groups, there did not appear to be an additive effect to the Acarbose alone effect.

In a separate study, the pharmacokinetics of combination therapy were examined. The dose of Acarbose used was associated with carbohydrate malabsorption in rats with increased food uptake and increased fecal excretion. With all three combination oral hypoglycemic agents, overall exposure was moderately influenced (decreased compared to treatment alone) probably due to reduced absorption induced by decreased gastrointestinal transit time in response to the high dose of Acarbose. This reduction in expected exposure may account for the lack of additive effects seen in study PH23643. It is not clear if the standard human dose of acarbose would result in similar findings with the combined therapy.

The results from these studies suggest that there is no significant toxicological interaction with Acarbose in combination with metformin, glybenclamide or chlorpropamide. On the contrary, these results indicate that there may be a diminution of the effect of the oral hypoglycemic agents in the presence of a high dose of Acarbose due to decreased gastrointestinal transit time. The pharmacokinetics of the combination of oral hypoglycemics and the low dose of Acarbose was not examined. There was no apparent increased toxicity when oral hypoglycemics were combined with the low dose of Acarbose.

Although these studies are not an exhaustive examination of combination therapy of Acarbose with oral hypoglycemics, they do indicate that there is not likely to be an enhancement of toxicological effects by the combination of these two types of agents. The doses tested, particularly for the oral hypoglycemics were not particularly active pharmacologically in the test animals, and suggest that there would be a diminution of effectiveness with the combined therapy. However, the most important results for efficacy will depend upon the outcome of clinical trials.

LABELING COMMENTS:

There are no specific additions to the labeling including results of animal studies with combination therapy. These are not necessary. However, the labeling should be updated to current standards of reporting carcinogenicity results. The current label indicates that nine chronic/carcinogenicity studies were performed. The only testing that is applicable in this section of the label would be the carcinogenicity (2 year studies in rodents) or which address specific issues of carcinogenicity A year-long dog study does not qualify for a carcinogenicity study. Therefore, the reference to the dog study should be removed, since it was not specifically a carcinogenicity study. The first paragraph of the Carcinogenicity section should read:

"Carcinogenesis, Mutagenesis, and Impairment of Fertility: Eight carcinogenicity studies were conducted with Acarbose. Six studies were performed in rats (two strains, Sprague-Dawley and Wistar) and two studies were performed in hamsters."

The rest of the Carcinogenicity section is adequate.

Specific mutagenicity studies should be listed. Our current records indicate findings from five studies that were reported. However, if additional studies were submitted (as indicated by the current label), they should be included in the listing. Suggested wording is as follows:

"Acarbose did not induce DNA damage *in vitro* in the CHO chromosomal aberration assay, bacterial mutagenesis (Ames) assay, or a DNA binding assay. *In vivo*, no DNA damage was detected in the dominant lethal test in male mice, or the mouse micronucleus test."

RECOMMENDATION

AP: Pharmacology recommends approval of NDA 20-482/S008. The following comments should be communicated to the sponsor regarding labeling revisions:

TO BE COMMUNICATED TO SPONSOR

Labeling should be updated to current standards of reporting carcinogenicity and mutagenicity results. The current label indicates that nine chronic/carcinogenicity studies were performed. The only testing that is applicable in this section of the label would be the carcinogenicity (2 year studies in rodents) or which address specific issues of carcinogenicity A year-long dog study does not qualify for a carcinogenicity study. Therefore, the reference to the dog study should be removed. The first paragraph of the Carcinogenicity section should read:

"Carcinogenesis, Mutagenesis, and Impairment of Fertility: Eight carcinogenicity studies were conducted with Acarbose. Six studies were performed in rats (two strains, Sprague-Dawley and Wistar) and two studies were performed in hamsters."

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"Acarbose did not induce DNA damage *in vitro* in the CHO chromosomal aberration assay, bacterial mutagenesis (Ames) assay, or a DNA binding assay. *In vivo*, no DNA damage was detected in the dominant lethal test in male mice, or the mouse micronucleus test."

/S/

3/16/98

Ronald W. Steigerwalt, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20482/S007/S008

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

Date: MAY 31 1998

NDA #:	NDA 20-482, SE1-007 and SE1-008
Applicant:	Bayer Corporation
Name of Drug:	Precose (acarbose)
Indication:	Adjunct to diet to lower blood glucose in patients with non-insulin dependent diabetes. It can also be used in combination with insulin or with a metformin
Document Reviewed:	Vol. 1-20, dated September 29,1997 Vol. 1 and 25-50, dated November 24, 1997
Statistical Reviewer:	Girish Aras Ph.D.
Medical Input:	Robert Misbin, MD
Key words:	Acarbose, Insulin, Sulfonylurea, Diabetes

Background

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. This review concerns supplements SE1-007 and SE2-008 which discuss efficacy of Precose in combination with insulin and metformin, respectively. The sponsor has submitted three and two adequate and well-controlled studies for supplements SE1-007 and SE2-008, respectively, one of them (626 Canada) being common to both and also to the original NDA 20-482 and was reviewed by CDER statistician Mr. Dan Marticello.

I. Introduction

This review focuses on trials D96-004 and D95-020. The other two trials (626) were reviewed by Mr. Marticello in a related but different context. These trials are reviewed here to augment his review in the context of current supplements.

Table 1 Study specification for SE1-007

Study number/Location	Study Design[1]	Study Period	Treatment Arm	Number of Patients
D96-004 US	DB P PC R MC	24 weeks	Acarbose 50-100 mg TID* Placebo	98 97
626[3] Canada	DB P PC R MC	52 weeks	Acarbose 50-200 mg TID Placebo	41 50

*Included a 25 mg TID titration dose

[1] Study design designated as follows: DB = Double-Blind; XO = Cross-Over; P = Parallel; R = Randomized; MC = Multi-center; PC = Placebo Controlled.

[2]Submitted in NDA 20-482, 9/2/94 Volumes 82-83.

[3] Submitted in NDA 20-482, 9/2/94, volumes 57-58.

Table 2 Study specification for SE1-008

Study number/Location	Study Design[1]	Study Period	Treatment Arm	Number of Patients
D95-020 US	DB P PC R MC	24 weeks	Acarbose 50-300 mg TID* Placebo	84 84
626[2] Canada	DB P PC R MC	52 weeks	Acarbose 50-200 mg TID Placebo	41[a] 42[a]

*Included a 25 mg TID titration dose

[1] Study design designated as follows: DB = Double-Blind; XO = Cross-Over; P = Parallel; R = Randomized; MC = Multi-center; PC = Placebo Controlled.

[2] Submitted in NDA 20-482, 9/2/94, volumes 57-58.

[a] Patients randomized in the metformin stratum only.

2 Page(s) Redacted

Confidential / TRADE
Secret
Confidential/
Commercial

B. STUDY D96-004

1. Study Objective

The objective of this study was to demonstrate the long-term efficacy, subjective tolerability and safety of acarbose as compared to placebo in patients with NIDDM inadequately controlled by insulin.

2. Study Design and Sample Size

This was a 26 week, multi-center, randomized, double-blind, placebo controlled, two arm, parallel group comparison study consisting of:

1) a two-week screening period
2) a 24-week double-blind, parallel treatment period of acarbose or placebo, with a forced titration from 25 mg tid to 50 mg tid after four weeks, and then titration after 12 weeks from 50 mg tid to 100 mg tid depending upon efficacy.

To detect a 0.7% difference between treatments in mean change from baseline in HbA_1c, the required sample size was estimated to be 73 per treatment group. The estimate was based on the two-tailed test between acarbose and placebo, an estimated standard deviation of 1.3%, a significance level of 0.05 and a power of 0.90. The sample size was adjusted to 85 patients per treatment group to allow for dropouts.

3. Patient Population

Ninety-seven and 98 patients were randomized to the placebo and Acarbose groups, respectively.

4. Demographics and Other Baseline Characteristics

Demographics and disease characteristics were compared for treatment groups for the intent-to-treat population as well as the efficacy evaluable population. Statistically, the treatment groups were comparable with respect to the variables listed: Age, Weight, BMI, Duration of NIDDM, sex and race. Efficacy variables at baseline for the efficacy evaluable population were comparable, except HDL cholesterol. Efficacy variables were HbA_1c, fasting plasma glucose, 60-min. plasma glucose, 90-min. plasma glucose, 120-min. plasma glucose, plasma glucose AUC, fasting triglycerides, 60-min. triglycerides,

90-min. triglycerides, 120-min. triglycerides, triglyceride AUC, total cholesterol, HDL cholesterol, LDL cholesterol, normalized urinary albumin, and normalized urinary glucose.

5. Primary Efficacy Endpoint

The primary efficacy variable was specified as the change from the baseline in HbA_1c at the end of the double blind period (visit 6, week 24). Baseline was defined as the Visit 1 (week 0) value for the variable. Analysis of variance was performed, as per protocol, with effects for treatment, investigator, and treatment-by-investigator interaction; if the treatment-by-investigator interaction effect was found to be nonsignificant, it was to be dropped from the model. Investigators were to have completed a minimum of two patients per treatment group for inclusion in the interaction model. The efficacy analysis was performed for the efficacy evaluable population as well as the intent-to-treat population. The efficacy evaluable population was considered as the primary population. Seventy-three (75.3% of the randomized) and 72 (73.5% of the randomized) patients were judged valid for efficacy from placebo and acarbose groups, respectively.

6. Efficacy Results

Acarbose was significantly superior to placebo (p=0.0001) in the primary analysis of HbA_1c change from baseline to the double-blind endpoint visit in the efficacy evaluable population. The size of the treatment effect was 0.69. Furthermore, at each visit, acarbose was superior to placebo (p<=0.0018). The results were similar in the intent-to-treat population. Acarbose was significantly superior to placebo at every visit (p<=0.0014) and at double-blind endpoint (p=0.0001). For both populations the treatment-by-investigator interaction was nonsignificant and was dropped from the final model.

Using the criteria of a decline in HbA_1c of at least 0.7%, the response rate in acarbose patients was 42% compared to 23% for placebo patients (p=0.01). Among placebo patients there were 19 whose efficacy data was excluded because of a change in insulin dose. There were 18 such acarbose-treated patients. Although not tabulated in the original submission, the Sponsor was asked to submit HbA_1c on these patients separately. In analyzing these data, the CDER medical reviewer Dr. Misbin scored a patient as 'better' if HbA_1c fell by >0.5% accompanied by a reduction in insulin dose. He scored a patient as 'worse' if HbA_1c rose by >0.5% accompanied by an increase in insulin dose. Patients were considered neither better nor worse if the level changed by 0.5% or less, or if the change in the level and change in insulin dose were in opposite directions. Results are as follows:

Table 5 Classification of patients excluded from efficacy evaluable population

	Placebo	Acarbose	P-value
Better	2	8	
worse	3	3	
neither	14	7	0.022*

* Fisher's exact, two sided exact test after combining 'worse' and 'neither' for each group

The above results show that exclusion of patients with changes in insulin dose from the primary efficacy analysis does not bias the results. Even patients whose insulin dose changes showed a net improvement on acarbose.

Other efficacy variables are summarized in the next table for the efficacy evaluable population.

Table 6 Change from baseline in Secondary Efficacy Variables

	LS Mean changes		
	Placebo	Acarbose	P-value
Fasting Plasma glucose(mg/dL)	8.87	-2.84	0.4221
60-min. plasma glucose(mg/dL)	8.03**	-27.99	0.0178
90-min. plasma glucose(mg/dL)	5.68**	-49.95	0.0004
120-min. plasma glucose(mg/dL)	6.51**	-55.32	0.0001
plasma glucose AUC	859.69**	-3964.2	0.0074
fasting triglycerides*	0.99	0.90	0.0546
60-min. triglycerides*	0.99	0.90	0.0617
90-min. triglycerides*	0.96**	0.83	0.005
120-min. triglycerides*	0.96**	0.82	0.0133
triglycerides AUC*	0.97**	0.86	0.0223
total cholesterol(mg/dL)	-2.98	-0.43	0.446
HDL cholesterol(mg/dL)	-0.44	-1.24	0.4341
LDL cholesterol(mg/dL)	-2.43**	6.83	0.0018
normalized urinary albumin*	1.23	1.13	0.5113
Normalized urinary glucose(g/day)	6.21**	-5.41	0.0074

*geometric LS mean of the ratio of the endpoint value to the baseline value

** Significantly different from acarbose ($p < 0.05$)

7. Safety results

Incidence of adverse events, by body system are reported in the table below provided they were statistically significant. Statistically significantly more acarbose than placebo patients experienced a treatment-emergent adverse event.

Table 7 Incidence of statistically significant adverse events, by body system

Body system	Placebo (n=96)	Aracbose (n=96)	P-value
Any body system	78	89	0.018
Digestive	39	74	0
Nervous	23	12	0.04

The incidence rates of events for which the difference between placebo and acarbose was statistically significant, and for selected other events, are listed below.

Table 8 Incidence of selected adverse events

Adverse Events	Placebo	Acarbose	P-value
Flu-Syndrome	3	11	0.026
Flatulence	25	68	0
Diarrhea	14	24	0.07
Abdominal Pain	5	7	0.55

There was a significantly greater rate of discontinuation due to adverse events in the acarbose group as compared to placebo (20% vs. 6%, respectively). The primary events leading to discontinuation in the acarbose group were flatulence, and to a lesser degree, diarrhea and abdominal pain.

8. Conclusions

Overall, this study demonstrates the long-term efficacy, subjective tolerability and safety of acarbose as compared to placebo in patients with NIDDM inadequately controlled by insulin. There were statistically significant adverse events, particularly, related to digestive system in patients treated with acarbose than with placebo.

C. STUDY 0626

This was the only study conducted outside of the U.S. that was considered to have met the criteria for an adequate and well-controlled study of acarbose in combination with insulin or metformin in type 2 diabetes. As mentioned in the background, this study has previously been reviewed by Mr. Marticello for the original NDA 20-482 which was

submitted in support of acarbose 50mg, 100mg, and 200mg oral tablets as an adjunct to diet or diet plus metformin therapy in the treatment of patients with NIDDM. However, it should be noted that this study was performed before acarbose was approved for marketing by FDA at dosages not to exceed 100mg TID. Mr. Marticello's review is summarized here with some additional comments and tables relevant to current applications.

This was a double-blind, placebo-controlled, stratified, randomized, group comparison study performed at eight centers in Canada. All patients had type 2 diabetes and were stratified, prior to randomization, into four strata according to background therapy: diet alone, diet plus sulfonylurea, diet plus metformin, and diet plus insulin. Following stratification, patients were randomized within their stratum to receive either placebo or acarbose 50-200 mg TID in combination with their background treatments (which could not be changed during the first six months of treatment). The study included a six-week pre-treatment period followed by a 52-week treatment period. Only the results of acarbose in combination with insulin (relevant for SE1-007) or with metformin (relevant for ES1-008) stratum will be presented here.

Patients initially received 50mg tid of their randomized treatment. They were then titrated upward or downward to 100mg 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 insulin or metformin which were not permitted until after the 24 week double-blind treatment time point. However, investigators were permitted to decrease the dosage of insulin and metformin. Patients who had such insulin or metformin dosage increases were included in the efficacy population only up the point of time of such increase. The criterion for validity for efficacy analysis was patients completing at least 60 days in the double-blind period. This was extended from the original eight weeks to make sure that patients were on treatment for at least two months, the time necessary to show early effect of therapy.

Table 9 Patient frequencies

Stratum	Intent-to-treat		Efficacy Analysis (HbA_1c)		Efficacy Analysis (Glucose AUC)	
	Acarbose	Placebo	Acarbose	Placebo	Acarbose	Placebo
Diet & Insulin	41	50	35	44	36	48
Diet & Metformin	41	42	35	39	35	40

1. Analysis for Diet & Insulin Stratum

The primary efficacy criteria were reduction from baseline of HbA_1c and in postprandial plasma glucose AUC (fasting subtracted) in the efficacy population following a standard meal. As seen in Table 10, a significant decrease in HbA_1c was not observed in the

acarbose-treated patients when compared to placebo-treated patients. In this study the investigators were not allowed to increase insulin dosage during the first six months of treatment, but could lower insulin dosage if necessary. It is of interest that insulin dosage decreased by 15% or more from baseline in 36.7% of patients on acarbose versus only 12.6 % of placebo patients. It is conceivable that the greater incidence of reductions in insulin dosage in the acarbose group could have partly offset the effects of acarbose in the study.

Acarbose therapy resulted in significant reductions from baseline in the incremental glucose AUC and in the 90 and 120 minute postprandial plasma glucose levels when compared to placebo. There was no effect on fasting glucose levels.

Table 10 HbA_1c and Plasma Glucose Results at Endpoint for Efficacy Population

Variable	Baseline	Mean Change from Baseline	Treatment Effect	P-value
HbA_1c				
Placebo	7.8	-0.2%		
Acarbose 50-200mg TID	7.7	-0.6%	-0.4%	0.0772[a]
Glucose AUC (mg*hr/dL)				
Placebo	155.9	9.1		
Acarbose 50-200mg TID	157.6	47.3	-56.4	0.0004[b]

[a] Nonsignificant at 0.05 level. To be compared with 0.025 due to Bonferroni correction for multiplicity.

[b] Significant at 0.05 level. To be compared with 0.025 due to Bonferroni correction for multiplicity.

2. Analysis for Diet & Metformin Stratum

The primary efficacy criteria were reduction from baseline of HbA_1c and in postprandial plasma glucose AUC (fasting subtracted) in the efficacy evaluable population following a standard meal. As seen in Table 11, a significant decrease in HbA_1c was observed in the acarbose-treated patients when compared to placebo-treated patients.

Acarbose therapy resulted in significant reductions from baseline in the incremental glucose AUC and in the 60, 90 and 120 minute postprandial plasma glucose levels when compared to placebo. There was no effect on fasting glucose levels.

Table 11 HbA_1c and Plasma Glucose Results at Endpoint for Efficacy Population

Variable	Baseline	Mean Change from Baseline	Treatment Effect	P-value
HbA_1c				
Placebo	7.9	0.3%		
Acarbose 50-200mg TID	7.8	-0.5%	-0.8	0.0106[a]
Glucose AUC (mg*hr/dL)				
Placebo	144	-4.3		
Acarbose 50-200mg TID	131.4	41.6	-37.3	0.0102[a]

[a] Significant at 0.05 level. To be compared with 0.025 due to Bonferroni correction for multiplicity.

3. Adverse events

As noted in Mr. Marticello's review and as in the trials previously reviewed here, the most commonly reported adverse events were flatulence, diarrhea, and abdominal cramps. The most common discontinuation reason was the reporting of an adverse event, the most common of which was flatulence. See Marticello's review for more details.

4. Conclusion

It should be noted that this study was performed before acarbose was approved for marketing by FDA at dosages not to exceed 100mg TID. However, the subset analysis restricting the dose levels to 100 mg is not presented here due to concern of introducing bias in the analysis. As far as efficacy of acarbose in combination with insulin is concerned (supplement SE1-007), as seen in Table 10, a significant decrease in HbA_1c was not observed in the acarbose-treated patients when compared to placebo-treated patients, however there was a trend in the right direction. On the second primary endpoint, Glucose AUC, statistical significance was observed. Acarbose was efficacious in combination with metformin (supplement SE1-008) on both primary endpoints. Acarbose was observed to be safe. Most commonly reported adverse events were flatulence, diarrhea and abdominal cramps.

D. STUDY D95-020

1. Study Objectives

The objective of this study was to demonstrate the long-term efficacy, subjective tolerability and safety of acarbose as compared to placebo in patients with type 2 diabetes inadequately controlled on either metformin 2000 mg/day or 2500 mg/day in divided doses.

2. Overall Study Design and Plan

This was a 31-week, multi-center, randomized, double-blind, placebo-controlled, two-arm, parallel-group comparison study consisting of:

1) a one-week screening period
2) a six-week, single-blind, placebo pre-treatment period
3) a 24-week, double-blind, parallel treatment period of acarbose or placebo, with a forced titration from 25 mg tid to 50 mg tid and titration of 50mg tid to 100 mg tid based on efficacy.

All patients were stabilized on diet plus metformin therapy at a dose level of 2000 mg to 2500 mg for a minimum of 56 days prior to screening. They continued on their metformin therapy throughout the duration of study. In addition, they received placebo during the six-week placebo run-in period. At randomization, they were given either acarbose or placebo according to the following schedule:

Week 0-4: 25 mg tid
week 4-12: 50 mg tid
Week 12-24: 50 mg tid
or
100 mg tid

The patient was titrated upwards to the 100 mg dosage level if his or her one-hour postprandial capillary blood glucose at Visit 6 was greater than 160 mg/dL. Patients unable to tolerate the 100 mg tid dose could have their dose of study medication reduced to 50 mg tid. Patients who were unable to tolerate the 50 mg tid dose were withdrawn from study participation. Patients were questioned about symptoms of possible hypoglycemia at clinic visits.

A total of 168 patients were randomized; 84 patients were randomized to the placebo group and 84 patients were randomized to acarbose therapy. Seventy-four (88%) patients in each group were valid for efficacy. The most common reasons for invalidity in each group were inadequate duration of treatment with study medication and one of the metformin doses (2000 or 2500 mg per day) was not taken for at least 56 days prior to screening.

3. Primary Efficacy Variable

The primary efficacy criterion in this study was the change from baseline (visit 3) in HbA_1c at double-blind endpoint, defined as the last valid observation after at least 56 days of double-blind treatment. Analysis of covariance was the primary statistical model employed with baseline as a covariate with effects for treatment, investigator, and treatment-by-investigator interaction; if the treatment-by-investigator interaction effect was found to be nonsignificant, it was to be dropped from the model. Investigators were to have completed a minimum of two patients per treatment group for inclusion in the interaction model

4. Demography

There were no clinically significant differences in demographic parameters between the placebo-treated and acarbose-treated groups. For patients valid for efficacy, the mean patient age was 55.9 years and 57.2 years, the mean fasting weight was 91.5 kg and 94.4 kg, the mean BMI was 32.3 kg/m^2 and 32.4 kg/m^2, and the mean duration of diabetes was 7.8 years and 7.2 years for the placebo-treated and acarbose-treated groups, respectively.

None of these differences were statistically significant. For patients valid for efficacy, the placebo group was 49% male and 80% Caucasian while the acarbose group was 61% male and 86% Caucasian; these also were not statistically significant differences.

Baseline efficacy variable values had a general tendency for greater severity at baseline in the acarboe group as compared to the placebo group with respect to glycemic control, as measured by HbA_1c, plasma glucose, and urinary glucose levels. The difference was statistically significant for 60-minutes postprandial plasma glucose. Baseline means for HbA_1c (%) was 8.17 and 8.46 for placebo and acarbose, respectively. In the intent-to-treat population, the baseline imbalance between treatments for HbA_1c was statistically significant.

5. Analysis of Efficacy

Acarbose was significantly superior to placebo (p=0.0001) in the primary analysis of HbA_1c mean change from baseline to the double-blind endpoint visit in patients valid for efficacy. These results are summarized below. Results for intend-to-treat population were similar. The placebo subtracted difference in HbA_1c at double blind endpoint was -0.71%.

Table 12 Analysis of Covariance, Efficacy Population

	Mean Change from Baseline			
Treatment	N	Adjusted mean	Placebo-subtracted Change from Baseline	P-value[a]
Placebo	74	0.08%		
acarbose	73[b]	-0.57%	-0.65%	0.0001

[a] Based on main effect model, since drug*investigator interaction effect was nonsignificant (p=.27)

[b] Although 74 patients were valid for efficacy for at least one of the several parameters, for this specific parameter, HbA_1c, because of missing laboratory value in one patient, there were 73 patients valid for efficacy.

6. Adverse Events

There was a statistically significantly greater incidence of digestive system events in the acarbose group (56%) than in the placebo group (29%). The incidence rates of events for which the difference between placebo and acarbose was statistically significant, and for selected other events, are listed below.

Table 13 Incidence of Selected Adverse Events

Adverse Event	Placebo	Acarbose
Flatulence*	4/84 (5%)	26/84 (31%)
Diarrhea	9/84 (11%)	14/83 (17%)
Abdominal Pain	5/84 (6%)	7/84 (8%)

* Statistically significant at 0.05

There were no deaths in the study. There was a significantly greater rate of discontinuation due to adverse events in the acarbose group as compared to placebo (12% vs. 4% respectively). The primary events leading to discontinuation in the acarbose group were diarrhea, and to a lesser degree, flatulence and abdominal pain.

7. Conclusion

The study confirmed the safety, tolerability and effectiveness of acarbose when combined with metformin and diet as therapy for type 2 diabetes. Mean changes in HbA_1c levels of the acarbose-treated patients were improved significantly as compared to the placebo-treated patients without introducing any increased risk of hypoglycemia, weight gain, liver function abnormality or other life-threatening conditions. The most prominent adverse event associated with acarbose therapy was flatulence.

III. overall conclusions

In study 0626, a significant decrease in HbA_1c was not observed in the acarbose-treated patients when compared to placebo-treated patients, however there was a trend in favor of acarbose. On the second primary endpoint, Glucose AUC, statistical significance was observed.

Supplement SE1-008: Studies D95-020 and 0626 support each other in showing that acarbose when combined with metformin and diet is efficacious and safe for patients with NIDDM. Diarrhea, flatulence and abdominal pain were the most prominent adverse events and were statistically related to acarbose.

/S/

Girish Aras, PhD

Concur: Dr. Sahlroot /S/ 5/22/98

Dr. Nevius /S/ 5/31/98

cc:
Orig. NDA 20-482/SE1-007, 008
HFD-510 / Division File
HFD-510 / SSobel, Rmisbin, JWeber
HFD-715 / Division File, Chron
HFD-715 / GAras, ENevius, TSahlroot

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20482/S007/S008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	20-482
Acarbose 50, 100 mg tablets (Precose®)	
Submission Date:	24 November 1997
Sponsor:	Bayer
Type of Submission:	Supplemental New Drug Application
Reviewer:	Michael J. Fossler

Submission

Acarbose is an α-glucosidase inhibitor indicated (either as monotherapy or in combination with a sulfonylurea) in the treatment of Type 2 diabetes. Acarbose acts within the intestinal lumen to inhibit the hydrolysis of starch to glucose. This results in a lowering of post-prandial glucose and improvement in long-term glycemic control. Since acarbose is a locally-acting drug and has low (2-4%) bioavailability, the effects of other drugs on its rate and extent of absorption are not generally considered to be an issue; however, acarbose itself may affect the absorption of other drugs.

The present submission is an efficacy supplement examining the efficacy of acarbose and metformin in combination in NIDDM patients. The mechanism of action of metformin is not completely understood, but it is felt to act on the liver to lower glucose production, as well as increase insulin sensitivity. It might be expected that the effects of metformin and acarbose might be additive, due to their different mechanisms of action. A small study in 6 normal volunteers suggested that acarbose significantly reduces the bioavailability of metformin when the two drugs are given concomitantly; therefore, it was necessary to determine whether or not a dose adjustment might be necessary when the two are used together.

Study D96-016 01: Effect of Acarbose (50 mg TID and 100 mg TID) on the Pharmacokinetics and Pharmacodynamics of Metformin (500 mg BID) in NIDDM patients

Study Design

This study was a randomized, double-blind, placebo-controlled two period crossover trial in 20 (17 completed) male and female NIDDM patients. Each period consisted of 5 in-clinic days designated as Day -2 to Day 3. Eligible subjects were discontinued from their other hypoglycemic medications for 5 days before starting the study. At least 2 days prior to the evening of Day -3, each subject was started on metformin 500 mg BID, which was continued for the duration of the study. The subjects were then randomized to receive either acarbose (one day of 50 mg TID with meals followed by 2 days of 100 mg with meals) or matching placebo. Plasma samples for the quanitiation of metformin were taken after the morning dose on Days 1 and 3. In addition, serum glucose and insulin levels were also measured. There was a 3 day washout between study periods, during which acarobse was discontiued, but metformin continued.

Results

Summary metformin pharmacokinetic data are shown in Table 2. The data indicate that the extent of absorption of metformin is not significantly altered by the co-administration of acarbose, but that the rate of absorption (as estimated by Cmax) is somewhat slower with the combination. Table 3 shows the plasma glucose results obtained from the study. The results indicate that this small change in absorption rate is unlikely to have any adverse effect on the clinical efficacy of the combination, as serum glucose is significantly lower for the treatment group as compared with placebo for both doses of acarbose (Day 1 used 50 mg TID, Day 3 used 100 mg TID). No change in the time of the glucose peak was seen between treatment and placebo.

Table 2: Mean metformin pharmacokinetic data from Study D96-016 01. Except where noted, values in the table are mean± SD (CV%)

Parameter	Day	Metformin Alone	Metformin + Acarbose	90% Confidence Intervals
AUC(0-τ)ss (ng•hr/ml)	Day 1	6897±2210 (32%)	5985±1694 (28%)	87.0 (82.8 - 91.3)
	Day 3	6383±2040 (32%)	5575±1963 (35%)	86.1 (80.7 - 91.8)
Cmax (ng/ml)	Day 1	1032±317 (31%)	841±241 (29%)	81.6 (77.2 - 86.2)
	Day 3	952±274 (29%)	786±277 (35%)	80.8 (75.6 - 86.5)
tmax (hrs)‡	Day 1	4 (1 - 4)	4 (2 - 6)	na
	Day 3	4 (1 - 4)	4 (1 - 8)	na
$t_{1/2}$ (hrs)	Day 1	4.8±1.8 (36%)	4.3±1.0 (24%)	na
	Day 3	4.3±1.2 (29%)	3.8±1.0 (26%)	na

‡median (min-max)

Table 3: Glucodynamic parameters from Study D96-016 01. Except where noted, values in the table are mean± SD (CV%). N.B.: Day 1 used 50 mg TID acarbose; Days 2 and 3 used 100 mg TID.

Parameter	Day	Metformin Alone	Metformin + Acarbose
3 hr. Avg. Blood Glucose (mg/dl)	Day 1	324±84.2 (25.9%)	283±72.7# (25.6%)
	Day 3	288±75.0 (26.0%)	244±73.0# (29.9%)
Cmax (mg/dl)	Day 1	351±79.9	297±74.5#
	Day 3	310±68.6	254±63.1#
tmax (hrs)‡	Day 1	87 (45-135)	86 (45-135)
	Day 3	75 (45-135)	84 (45-165)

‡median (min-max)
#significantly different from metformin alone ($p < 0.001$)

Confirmation of the above results was obtained from one of the pivotal efficacy trials, D95-020. This was a 24-week, randomized, placebo-controlled, double-blind parallel-group comparison study in NIDDM patients given either metformin + acarbose or matching placebo. Plasma samples were drawn at Weeks 4, 12, and 24 just before the morning dose of metformin (trough levels) and at two hours post-prandial ("peak" levels). The data are shown in Table 4. The results indicate that there is no clinically significant interaction between acarbose and metformin.

Table 4: Mean ± SD peak and trough metformin levels obtained as part of Study D95-020. Number of patients/group ranged between 49 and 79.

	Baseline	Week 4	Week 12	Week 24
Peak (2 hours post-prandial) Metformin levels (ng/ml)				
Metformin + Placebo	1815±636	1772±729	1839±681	1732±563
Metformin + Acarbose	1784±580	1699±605	1745±724	1605±683
Ratio (90% CI)	not computed	0.98 (0.79 - 1.22)	0.95 (0.74 - 1.21)	0.89 (0.73 - 1.07)
Trough Metformin levels (ng/ml)				
Metformin + Placebo	564±356	571±399	625±443	572±442
Metformin + Acarbose	508±295	603±466	647±572	562±363
Ratio (90% CI)	not computed	0.93 (0.84 - 1.04)	0.91 (0.79 - 1.05)	0.87 (0.75 - 1.02)

Conclusion

1) The results of both studies in this sNDA clearly indicate that there is no clinically significant interaction between acarbose and metformin.

Recommendations

The clinical pharmacology and biopharmaceutics portion of sNDA 20-482 is approved. The proposed labeling under **Pharmacokinetics** is acceptable.

/S/ 5/20/98

Michael J. Fossler, Pharm.D., Ph.D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/

CC: NDA 20-482(orig., 1 copy), HFD-510(Misbin, Weber), HFD-850(Lesko), HFD-870(M.Chen, Fossler, Ahn), Central Document Room(Barbara Murphy)
2/24/98

Recommendation Code: AP

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20482/S007/S008

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

The following information is hereby provided pursuant to 21 U.S.C. § 505(c)(1) and 21 C.F.R. § 314.70(e):

Patent Number:	US Pat. No. 4,904,769
Expiration Date:	February 27, 2007
Type of Patent:	Drug product, formulation
Name of Patent Owner:	Bayer Aktiengesellschaft, Fed. Rep. of Germany
Agent/Applicant:	Bayer Corporation, residing in the US

The undersigned declares that Patent No. 4,904,769 covers the drug composition and pharmaceutical composition (formulation) of acarbose, which is the subject of this application for supplemental approval.

Carl E. Calcagni, R. Ph.
Vice President, Regulatory Affairs
Pharmaceutical Division
Bayer Corporation

EXCLUSIVITY SUMMARY for NDA # 20-482 **SUPPL #** S-007

Trade Name PRECOSE **Generic Name** acarbose TABLETS

Applicant Name BAYER **HFD-** 510

Approval Date _____

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 questions about the submission.

   a) Is it an original NDA? YES /___/ NO /✓/

   b) Is it an effectiveness supplement? YES /✓/ NO /___/

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

   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 /✓/ 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 /___/ NO /✓/

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

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /✓/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /___/

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

NDA # 20-482 PRECOSE (acarbose)

NDA # _____ _____

NDA # _____ _____

2. Combination product. NOT Applicable

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 /___/

If "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 9. IF "YES," GO TO PART III.

PART III <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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."

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

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 9:**

_____

_____

(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? If not applicable, answer NO.

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:

Investigation #1, Study # 026

Investigation #2, Study # 009

Investigation #3, Study # 004

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 #1 026 YES /✓/ NO /___/ Canada

Investigation #2 009 YES /✓/ NO /___/ non-USA

Investigation #3 004 YES /✓/ NO /___/ USA

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

NDA # 20-482 Study # 026

NDA # _____ Study # _____

NDA # _____ Study # _____

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 /✓/

Investigation #3 YES /___/ NO /✓/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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"):

Investigation #1, Study # 009

Investigation #2, Study # 004

Investigation #3, Study # _____

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 form 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 for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 #009

YES /✓/ Explain _____ NO /___/ Explain _____

Conducted outside U.S. _____

_____ _____

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: _____

_____

_____

/S/ _____ 9/24/98

Signature of preparer Date

Title: PM/CSO

APPEARS THIS WAY
ON ORIGINAL

/S/ _____ 9/28/98

Signature of Division Director Date

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA
HFD- /Division File
HFD- /CSO
HFD-85/Mary Ann Holovac

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98

EXCLUSIVITY SUMMARY for NDA # 20-482 **SUPPL #** 008

Trade Name PRECOSE **Generic Name** ACARBOSE TABLETS

Applicant Name BAYER **HFD-** 510

Approval Date _____

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 questions about the submission.

   a) Is it an original NDA? YES /___/ NO /✓/

   b) Is it an effectiveness supplement? YES /✓/ NO /___/

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

   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 /✓/ 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 /___/ NO /✓/

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

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /✓/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /___/

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

NDA # 20-482 (Precose) _____

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 /___/

If "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 9. 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."

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

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 9:**

_____

_____

(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? If not applicable, answer NO.

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:

Investigation #1, Study # 026 + METFORMIN

Investigation #2, Study # 020

Investigation #3, Study # _____

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 /✓/ 026 NO /___/

Investigation #2 YES /___/ 2020 NO /✓/

Investigation #3 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:

NDA # 20-782 Study # 026
NDA # _____ Study # _____
NDA # _____ Study # _____

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 /—/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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"):

Investigation #2, Study # 020

Investigation #__, Study # _____

Investigation #__, Study # _____

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 form 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 for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in 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: _____

_____

_____

/S/ 9/24/98

Signature of preparer Date

Title: CSO

/S/ 9/28/98

Signature of Division Director Date

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA
HFD- /Division File
HFD- /CSO
HFD-85/Mary Ann Holovac

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-482 Supplement # 007 008 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-510 Trade and generic names/dosage form: PRECOSE TABS (acarbose) Action: AP AE NA

Applicant BAYER Therapeutic Class ORAL HYPOGLYCEMIC

Indication(s) previously approved treatment of Type 2 diabetes – monotherapy

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ✓

Proposed indication in this application 007 - patients ≥ type 2 DM treated ≥ DIET plus insulin
008 - " " " " " " " " " plus METFORMIN

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ✓No (Sign and return the form) not for combination use

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___Neonates (Birth-1month) ___Infants (1month-2yrs) ___Children (2-12yrs) ___Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, attach memo describing status of discussions.

APPEARS THIS DAY ON ORIGINAL

___ d. 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 ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes ✓No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from /S/ (e.g., medical review, medical officer, team leader)

/S/ 9/23/98
Signature of Preparer and Title Date

Orig NDA/~~BLA~~ # 20-482 /S-007, S-008
HFD-510 /Div File
NDA/~~BLA~~ Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

Debarment Statement:

Bayer Corporation Pharmaceutical Division certifies 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 NDA #20-482.

Carl E. Calcagni, R.Ph.
Vice President, Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-482/S-008

DEC - 1 1997

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

Attention: Richard J. Fanelli, Ph.D.

Dear Dr. Fanelli:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	PRECOSE® (Acarbose) Tablets
NDA Number:	20-482
Supplement Number:	S-008
Date of Supplement:	November 24, 1997
Date of Receipt:	November 25, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on January 24, 1998, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-482/008
HFD-510/Div. Files
HFD-510/CSO/M. Johnston

filename: C:\DATA\WPFILES\20482ACK

SUPPLEMENT ACKNOWLEDGEMENT

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-482/S-007

BAYER CORPORATION, INC.
400 Morgan Lane
Wesr Haven, CT 06516

OCT 3 1997

Attention: Lee Scaros, Pharm.D., Associate Director, Regulatory Affairs

Dear Dr. L. Scaros:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: PRECOSE (Acarbose) Tablets

NDA Number: 20-482

Supplement Number: S-007

Date of Supplement: September 29, 1997

Date of Receipt: September 30, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on November 29, 1997, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely.

/S/

Ehid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-482/S-007
HFD-510/Div. Files
HFD-510/CSO/M. Johnston

filename:

SUPPLEMENT ACKNOWLEDGEMENT

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

July 7, 1998

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products
Office of Drug Evaluation II (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: DOCUMENT CONTROL ROOM 14B-04
5600 Fishers Lane
Rockville, MD 20857

RE: NDA #20-482 / S-007 & S-008 Precose® (acarbose) tablets
General Correspondence: Revised Package Insert

Dear Dr. Sobel:

With this submission, Bayer Corporation Pharmaceutical Division provides a revised package insert, as discussed with Dr. Robert Misbin during our teleconference on July 6, 1998. This package insert contains all of the revisions agreed to in consultation with the Division, regarding our two supplemental NDAs for Precose® tablets: NDA #20-482/S-007: "Use of Precose® in patients with type 2 diabetes treated with diet plus insulin", submitted September 29, 1997; and NDA #20-482/S-008: "Use of Precose® in patients with type 2 diabetes treated with diet plus metformin", submitted November 24, 1997.

Please do not hesitate to contact me at (203) 812-2010 if there are any further questions.

Sincerely,

Richard J. Fanelli, Ph.D.
Associate Director
Regulatory Affairs

/RJF

Desk copies: Robert I. Misbin, M.D., Medical Officer
Jena M. Weber, Consumer Safety Officer

Bayer

ORIGINAL

SUPPL NEW CORRES

Pharmaceutical Division
SE1-007
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2000

June 18, 1998

Pharm issues addressed. Labeling proposals are acceptable.
/S/ 7/1/98

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products
Office of Drug Evaluation II (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: DOCUMENT CONTROL ROOM 14B-04
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUN 19 1998
HFD-510

RE: NDA #20-482/S-007 & S-008 Precose® (acarbose) tablets
General Correspondence
- **Response to FDA Reviews**
- **Safety Update**

Dear Dr. Sobel:

With this submission, Bayer Corporation Pharmaceutical Division provides responses to all of the reviews and requests we have received from the Division to date, regarding our two supplemental NDAs for Precose® tablets: NDA #20-482/S-007: "Use of Precose® in patients with type 2 diabetes treated with diet plus insulin", submitted September 29, 1997; and NDA #20-482/S-008: "Use of Precose® in patients with type 2 diabetes treated with diet plus metformin", submitted November 24, 1997. These responses include new changes to the Description, Pharmacokinetics, Clinical Trials, and Carcinogenesis sections of the draft package insert. In addition, a Safety Update has been provided, covering the period of April 1, 1997 until May 20, 1998. Each of these issues are described in more detail below.

Noted
/S/ 6/30/98

In response to the Chemistry Review, which was received by FAX from Mr. Michael Johnston on March 16, 1998, we agree to make the two revisions to the Description section of the package insert. These changes include placing italics in the chemical name, and revising the structure

The Pharmacology Review Comments, signed by Dr. R.W. Steigerwalt and received by FAX from Mr. Johnston on March 18, 1998, requested revisions to labeling to reflect current standards of reporting carcinogenicity and mutagenicity results.

On May 5, 1998, a FAX was received from Ms. Jena Weber, which included a statement that the that metformin levels were reduced slightly in patients on acarbose, and that this should be included in the labeling. The basis for the statement that the amount of metformin absorbed was bioequivalent whether patients were taking acarbose or placebo, is in the results of study D96-016 in which the metformin AUC ratio was 0.87 (metformin + acarbose vs. metformin + placebo), with 90% confidence limits of 0.828 - 0.913. Since the confidence limits are within

the range of 0.80 - 1.25, the two treatments (metformin + acarbose and metformin + placebo) may be considered bioequivalent with respect to AUC according to standard FDA guidelines. Therefore, the Drug-Drug Interactions section has been revised to clarify that the amount of metformin absorbed while taking Precose® was bioequivalent to the amount absorbed when taking placebo, as indicated by the plasma AUC values

Included in the FAX sent on May 5, 1998, were comments regarding the Clinical Trials section of the package insert. As suggested in this FAX, we have revised table 2, included a figure from study 0626, and retained information about insulin treatment.

As the final item in this response, we provide a Safety Update, covering the period of April 1, 1997 until May 20, 1998, as requested by Mr. Johnston during our phone conversation on April 29, 1998 This Safety Update contains the recent Periodic Safety Update Report prepared by the Drug Safety International department of Bayer AG in Wuppertal, Germany , and a Safety Update prepared by Bayer Corporation Pharmaceutical Division Safety Assurance department in West Haven, CT . There are no new safety issues raised in these reports.

With this submission, it is our understanding that we have provided responses to all of the reviews and requests we have received from the Division to date. We look forward to hearing your feedback to this submission. Please do not hesitate to contact me at (203) 812-2010 if you have any questions.

Sincerely,

Richard J. Fanelli, Ph.D.
Associate Director
Regulatory Affairs

Desk copies: Robert I. Misbin, M.D., Medical Officer
Jena M. Weber, Consumer Safety Officer

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

NEW DRUG APPLICATION
SE1-007 BL
SE1-008 BL

ORIGINAL

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2000

February 13, 1998

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products
Office of Drug Evaluation II (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: DOCUMENT CONTROL ROOM 14B-04
5600 Fishers Lane
Rockville, MD 20857

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
FEB 17 1998
HFD-510

RE: NDA #20-482/S-007 & S-008 Precose® (acarbose) tablets
Response to FDA Request: Revised Draft Package Insert

Noted see

APPEARS THIS WAY ON ORIGINAL

Dear Dr. Sobel:

As requested by Mr. Michael Johnston, Bayer Corporation Pharmaceutical Division hereby submits five (5) copies of the revised draft package insert for our two supplemental NDAs for Precose® tablets: NDA #20-482/S-007: "Use of Precose® in patients with type 2 diabetes treated with diet plus insulin", submitted September 29, 1997; and NDA #20-482/S-008: "Use of Precose® in patients with type 2 diabetes treated with diet plus metformin", submitted November 24, 1997. The changes included in the Special Supplement - Changes Being Effected of December 22, 1997 (NDA #20-482/S-009), which was approved on February 4, 1998, have been incorporated into this revision.

Please do not hesitate to contact me at (203) 812-2010 if you have any questions.

Sincerely yours,

Richard J. Fanelli, Ph.D.
Associate Director
Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

LTF
/S/
2/17/98

NDA NO. 20482 REF. NO. 008
NDA SUPPL FOR SC1

ORIGINAL
NDA SUPPLEMENT

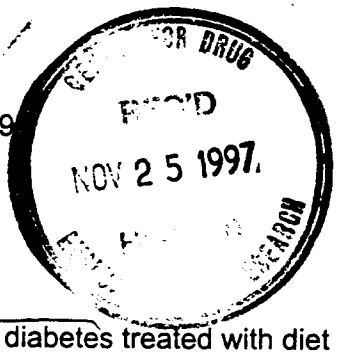
Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2000

November 24, 1997

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products
Office of Drug Evaluation II (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, MD 20857



will review
my copy
/S/
12/12/97

RE: NDA #20-482 (Precose®)
Supplemental New Drug Application
Use of Precose® in patients with type 2 diabetes treated with diet plus metformin

Dear Dr. Sobel:

Bayer Corporation, Pharmaceutical Division hereby submits a supplement to NDA #20-482 Precose® (acarbose) tablets. This supplement provides adequate clinical documentation to demonstrate the safety and efficacy for the use of acarbose in type 2 diabetes treated with diet plus metformin. Included in this supplement are revisions to the CLINICAL PHARMACOLOGY, CLINICAL TRIALS, INDICATION AND USAGE, PRECAUTIONS, ADVERSE REACTIONS, as well as DOSAGE AND ADMINISTRATION sections of the package insert. These revisions also include those that were submitted with the previous supplement supporting the use of Precose® in type 2 diabetics treated with diet plus insulin (NDA #20-482/S-007; submitted September 29, 1997). As discussed with the Division of Metabolism and Endocrine Drug Products in a telephone conversation on November 3, 1997, it is our understanding that the Division plans to review both the PRECOSE®/insulin and PRECOSE®/metformin SNDAs simultaneously.

The current supplement consists of an archival copy containing 90 volumes. A diskette containing the HbA1c data has been included with the archival copy of this supplement and with the review copy of Statistical Section, Section 10.

/S/
Acceptable (no concerns)
11-DEC-1997

Please refer to the attached Form FDA 356h and accompanying index for details of the complete contents of this supplement. A copy of the chemistry, manufacturing and controls section and the summary section have been sent to Mr. Richard Penta of the FDA District Office in Stoneham, MA. Please do not hesitate to contact me at (203) 812-2010 should questions arise.

Sincerely,

Richard J. Fanelli, Ph.D.
Associate Director, Regulatory Affairs

Desk Copies for:
~~Mr. Michael~~ Johnston, R.P.h.
Project Manager

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

NAI
/S/
12/12/97

SE1-007 Bm

ORIGINAL

NDA SUPPL AMENDMENT

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

October 20, 1997

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products
Office of Drug Evaluation II (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG REC'D OCT 21 1997 HFD-510 EVALUATION AND RESEARCH

RE: NDA #20-482/S-007 (Precose®)
Use of Precose® in Patients With Type 2 Diabetes Treated With Diet Plus Insulin
- General Correspondence
- Response to Request For Information

Dear Dr. Sobel:

Reference is made to Dr. Misbin's October 13, 1997 request for additional information. Dr. Misbin noted that the 1st paragraph of page 55 in volume 6 of the supplement 007 discussed several patients which were excluded from the efficacy analysis because their insulin dose had been changed. Although this exclusion is appropriate, as per the study protocol, Dr. Misbin expressed interest in reviewing the data for those individual patients who had a change in their insulin dose.

Attached for the Division of Metabolism and Endocrine Drug Products' review, please find two sets of data listings providing HbA1c and insulin dose data.
- Appendix #1 provides HbA1c and insulin dose data for all patients
- Appendix #2 provides HbA1c and insulin dose data for patients who had a change in their insulin dose (19 placebo patients and 18 acarbose patients).

Please do not hesitate to contact me at (203) 812-2693 should questions arise or if additional information is desired regarding those patients who had a change in their insulin dose.

Sincerely,

Lee Scaros

Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs
/LPS

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Desk Copies for:
Dr. Robert Misbin

SE1 S-007

DESK COPY Mr. Michael Johnston
R. Ph., Project Manager

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
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Phone: 203 937-2000

September 29, 1997

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products
Office of Drug Evaluation II (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA #20-482 (Precose®)
Supplemental New Drug Application
Use of Precose® in patients With type 2 diabetes treated with diet plus Insulin

Dear Dr. Sobel:

Bayer Corporation, Pharmaceutical Division hereby submits a supplement to NDA #20-482 Precose® (acarbose) tablets. This supplement provides adequate clinical documentation to demonstrate the safety and efficacy for the use of acarbose in type 2 diabetes treated with diet plus insulin. Included in this supplement are revisions to the CLINICAL PHARMACOLOGY, CLINICAL TRIALS, INDICATION AND USAGE, PRECAUTIONS, ADVERSE REACTIONS, as well as, DOSAGE AND ADMINISTRATION sections of the package insert.

This supplement consists of an archival copy containing 60 volumes. A diskette containing the HbA1c data has been included with the archival copy of the supplement and with the review copy of Statistical Section, Section 10.

Please refer to the attached Form FDA 356h and accompanying index for details of the complete contents of this supplement. Please do not hesitate to contact me at (203) 812-2693 should questions arise.

Sincerely,

Lee Scaros

Lee Scaros, Pharm.D.
Associate Director, Regulatory Affairs
/LPS

Desk Copies for:
Mr. Michael Johnston, R.Ph., Project Manager