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NDA 20-682

1 OF 2

NDA 20682



NDA 20-682

Bayer Corporation Pharmaceutical Division
Attention: Maureen H. Garvey, Ph.D.
Associate Director, Regulatory Affairs
400 Morgan Lane
West Haven, Connecticut 06516-4175

DEC 18 1996

Dear Dr. Garvey:

Please refer to your December 28, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glyset™ (miglitol) Tablets; 25, 50, and 100 mg.

We acknowledge receipt of your amendments dated January 30, February 7, April 26 and 29, May 1, 8, 10, and 13, June 4, and 18 (2), July 2 (2), August 2, 12, 16, and 30, September 18, October 11, 23, and 29, November 12, and December 11, 17, and 18, 1996.

This new drug application provides for the use of Glyset Tablets as an adjunct to diet or diet plus sulfonylurea therapy to improve glycemic control in patients with non-insulin-dependent diabetes mellitus (Type II).

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

The final printed labeling (FPL) must be identical to the draft physician labeling submitted on December 18, 1996, bottle labeling dated December 28, 1995, and blister labeling dated October 11, 1996. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 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 "FINAL PRINTED LABELING" for approved NDA 20-682. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

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

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

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

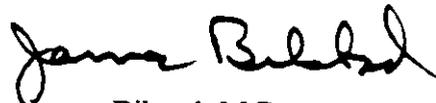
Please submit one market package of the drug product when it is available.

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

If you have any questions, please contact:

Julie Rhee
Consumer Safety Officer
(301) 443-3510

Sincerely yours,



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

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE
ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE
PUBLIC.

Section 13: The following information is hereby provided pursuant to 21 CFR 314.53(c):

Patent Number: U.S. Patent No. 4,639,436

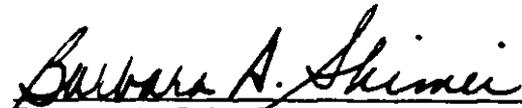
Expiration Date: 27 January 2004

Type of patent: drug, drug product, method of use

Name of patent owner: Bayer AG

Agent: applicant (Bayer Corporation) resides in the US

The undersigned declares that Patent No. 4,639,436 covers the formulation, composition, and method of use of miglitol. This product is the subject of this application for which approval is being sought.



Barbara A. Shimei, Esq.
Attorney for Applicant

EXCLUSIVITY SUMMARY for NDA # 20-682 SUPPL # _____

Trade Name Glyset Generic Name atorvastatin tablets

Applicant Name Parke-Davis Pharmaceutical 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 /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

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

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

YES /X/ NO /___/

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

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

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

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

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

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

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

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

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

YES /___/ NO /_X_/

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

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

NDA # _____

NDA # _____

NDA # _____

2. Combination product.

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 /_X_/

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 8. IF "YES," GO TO PART III.

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

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

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 8.

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

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 8:**

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

YES /___/ NO /___/

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

Investigation #2, Study # _____

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 /___/	NO /___/
Investigation #2	YES /___/	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 # _____ Study # _____
 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 #__, Study # _____

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 _____

**Pharmaceutical
Division**

September 18, 1996

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

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
ATT: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857

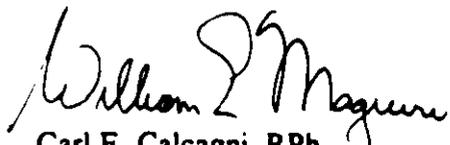
**RE: NDA 20-682
Glyset™ (miglitol tablets)
Debarment Statement**

Dear Dr. Sobel:

Bayer Corporation, formerly Miles Inc., 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 20-682.

If you have any questions regarding this information, please contact Maureen Garvey, PhD at (203) 812-5145.

Sincerely,

 ^{for}
Carl E. Calcagni, RPh
Vice President, Regulatory Affairs

CEC:bak



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

NDA # 20-682 Trade (generic) names Glyset (miglitol) Tablets

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

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

___ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Glyset is indicated as an adjunct to diet to improve glycemic control in NIDDM patients, and not for pediatric population

Julie Flier
Signature of Preparer

12-3-96
Date

cc: Orig NDA
HFD- /Div File
NDA Action Package

NDA 20-682 Glyset™ (miglitol) Tablets

This NDA was not presented to any Advisory Committee

NDA 20-682 Glyset™ (miglitol) Tablets

No applicable Federal Register notice was published for Glyset.

JUL - 8 1996

MEDICAL OFFICER'S REVIEW

of a

NEW DRUG APPLICATION

NDA 20-682

Generic name: MIGLITOL

Proposed trade name: GLYSET

Sponsor: BAYER

Pharmacologic Category: Alpha-glucosidase inhibitor

Proposed indication(s): Non-insulin dependent diabetes mellitus
Monotherapy or in combination with sulfonylureas

Dosage form: 25, 50, 100 mg tablets for oral administration

Related Drugs: Acarbose

original NDA submitted 1/22/96

response to inquiries submitted 2/7/96 and 5/8/96

safety update submitted 4/26/96

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INTRODUCTION

Miglitol is an oral alpha-glucosidase inhibitor for use in the management of postprandial hyperglycemia in patients with non-insulin dependent diabetes mellitus (NIDDM). It is administered with the first bite of each meal to delay the absorption of complex carbohydrates. The NDA seeks the indication for miglitol as monotherapy in patients with NIDDM not adequately treated with diet alone and in NIDDM patients who are not adequately treated with sulfonylureas. Miglitol's activity is similar to that of acarbose, a first generation alpha-glucosidase inhibitor which was approved for treatment of NIDDM at the end of 1995. The major difference between acarbose and miglitol is in systemic absorption. With acarbose, only about 2% of an oral dose is absorbed. By contrast, 50% of a 100 mg oral dose of miglitol is absorbed. The percent absorption is greater at lower doses. Despite the greater systemic exposure to drug, the incidence of systemic toxicity (increased liver transaminase levels) appears to be less with miglitol than with acarbose. Otherwise the efficacy and tolerability of the two drugs are similar.

CLINICAL PHARMACOLOGY

The site of action of miglitol is the brush border of the intestine. Therefore the extent of drug absorption and the blood levels attained are not directly related to its pharmacological effect. The pharmacokinetics properties of miglitol are therefore of primary use in evaluating systemic exposure for issues relating to safety rather than to efficacy. The systemic absorption of a 100 mg miglitol tablet or 100 mg oral suspension is approximately 50%. A greater percent absorption is observed with smaller doses. The elimination half life is generally 2-3 hours. Miglitol undergoes no metabolism either in the gut or systemically. Following intravenous administration of radiolabeled substance, urinary recovery of unchanged drug is nearly 100%. The elimination of miglitol is dependent on renal function. Increased plasma levels are observed when the drug is given to patients with renal insufficiency. Miglitol should not be used in this population of patients because the full dosage is required for therapeutic effect regardless of the plasma level. Dosage adjustment based on renal function is not an option. No significant effects of age, race, gender or hepatic disease on systemic pharmacokinetics have been observed. Miglitol may interfere with the absorption of glyburide and metformin. With respect to glyburide the AUC and C max was reduced 25% and 17% respectively. With metformin, the AUC and Cmax were reduced by 13% and 12% respectively. No interaction with digoxin warfarin or nifedipine has been found.

The clinical trials formulation is different from the to-be-marketed formulation and the Sponsor has not reported any bioequivalence studies. They have asked for a waiver based on the extreme aqueous solubility of the drug substance, and because the in vitro dissolution rates of the two formulations were virtually identical in water, simulated gastric fluid and simulated intestinal fluid. Also, since the site of action is within the lumen of the intestinal, a standard pharmacokinetics study comparing blood levels of drug would not necessarily predict how the two formulations would affect glucose absorption in patients.

OVERVIEW OF PHASE 3 STUDIES

The Sponsor has submitted eight controlled clinical trials which serve as pivotal studies and support the safety and efficacy of miglitol in the treatment of the hyperglycemia of NIDDM. There are five pivotal studies which evaluated miglitol as monotherapy and three which evaluated miglitol in combination with sulfonylureas (see table). All patients had NIDDM which was not adequately controlled by background therapy, of diet alone, or diet plus a sulfonylurea. All these studies were placebo-controlled randomized double-blind studies of parallel group design. All had a placebo run-in (pretreatment) phase and utilized HbA1c as the primary measure of efficacy. Fasting and postprandial glucose, insulin, and lipid levels were secondary measures of efficacy. Central laboratories were employed in most studies especially for determination of HbA1c, insulin and lipid measurements. HbA1c was measured by the Diamat assay with normal ranges comparable to DCCT reference assay. Drug effect is expressed as the change in HbA1c (as % of total hemoglobin) or plasma glucose on miglitol (final measurement minus baseline) minus the change on placebo (final measurement minus baseline). With respect to measures of adverse events, special emphasis was placed on frequent measurement of liver function tests, especially SGOT/SGPT because of the previous experience with acarbose. Because of concerns about malabsorption in patients on miglitol, the one year studies also measured serum iron, iron binding capacity, magnesium, folate, and vitamins B6, B12, and 25-OH vitamin D. Serum calcium, phosphorous, and albumin were also measured as part of routine clinical chemistries.

There are additional studies whose data have not yet been included in the NDA. These are:

There are also three extension trials X92-006, X92-009, and X92-014 of patients who completed studies D92-006, D92-009, and D92-014 respectively.

The application contains data from five pivotal studies which demonstrate the efficacy of miglitol as monotherapy and three pivotal studies of miglitol in combination with sulfonylureas (see table). Other non-pivotal controlled studies of miglitol as monotherapy are D83-077 and D83-113 (USA), 0264 (France), 0277 (Italy) and miglitol with a sulfonylurea is 0272 (Finland). There are also two small short term US studies of miglitol in IDDM , D83-078 and D83-112, and four European studies of NIDDM patients on insulin, 0273 and 0274 and two studies of patients with mixed diabetic background, 0278 and 0283.

MONOTHERAPY

Study Number	Miglitol Doses (mg tid)	Duration (weeks)	Miglitol Patients Valid for Efficacy
U.S. Studies			
D87-056 (0295)	50 and 100	14	108
D92-009 (0317)	50	56	104
Non-U.S. Studies			
0281 NL	25, 50, 100 and 200	24	253
G D, CH, CR	50 and 100	24	230
0307	100	24	40

Patient years.

29

112

117

106

18

WITH A SULFONYLUREA

Study Number	Miglitol Doses (mg tid)	Duration (weeks)	Miglitol Patients Valid for Efficacy
U.S. Studies			
D87-057 (0296)	50 and 100	14	115
D92-006 (0314)	25, 50 and 100	52	253
Non-U.S. Studies			
0306	100	24	48

31

253

22

SUMMARY OF EFFICACY

Monotherapy in NIDDM Patients:

There are five pivotal studies of NIDDM patients on diet alone of which two, D92-009 and D87-056, were performed in the United States. D87-056 was a 14 week study comparing placebo to miglitol 50 mg tid and 100 mg tid with 51-58 patients in each treatment arm. Study D92-009 was a 56 week study of miglitol 50 mg tid (n=104) vs placebo (n=98). As will be discussed later this study also compared miglitol 50 mg tid to Glyburide 2.5 mg bid and a combination of miglitol and glyburide. As shown in the tables, miglitol treatment resulted in a significant reduction of HbA_{1c}, fasting plasma glucose, 1 hr postprandial glucose, and 1 hour postprandial insulin but did not affect the fasting insulin level. The reduction of HbA_{1c} at 50 mg tid was 0.58 units in D92-009 and 0.69 units in D87-056.

US Adequate and Well-Controlled Studies Monotherapy in NIDDM Patients

US # (Int. #) Country	Duration of Treatment	Treatment Group*	Number of Patients†				Male (%)	Caucasians (%)	Mean Age (yr)	Mean BMI (Kg/m ²)	Mean Duration of NIDDM (yr)
			R	V	DC						
					AE	LE					
D92-009 (0317) US	56 weeks	Placebo	108	98	10	17	63	80	56	32	4.5
		Miglitol 50 mg	113	104	13	6	52	76	55	31	3.6
		Glyburide 2.5 mg bid	109	99	14	4	62	78	54	32	4.5
		Miglitol & Glyburide	112	103	20	0	49	86	56	32	4.1
D87-056 (0295) US	14 weeks	Placebo	69	58	4	4	45	60	56	30	6.7
		Miglitol 50 mg	66	57	4	2	47	70	56	31	5.5
		Miglitol 100 mg	63	51	6	3	51	67	58	33	5.4

* Dosages of miglitol tid.

† R = randomized; V = valid for efficacy; DC = discontinuations; AE = due to adverse events; LE = due to lack of efficacy.

US Adequate and Well-Controlled Studies
 Monotherapy in NIDDM Patients
 Mean HbA_{1c}, Plasma Glucose and Serum Insulin

Study	D92-009 (0317)			D87-056 (0295)			
	Baseline	Change	Treatment effect	Baseline	Change	Treatment effect	
HbA_{1c} (%)							
Placebo	7.86	+0.71		8.72	+0.47		
Miglitol	50 mg tid	7.92	+0.13	-0.58*	8.67	-0.22	-0.69*
	100 mg tid				8.51	-0.28	-0.75*
Fasting plasma glucose (mg/dl)							
Placebo	171	+33.8		195	+18.9		
Miglitol	50 mg tid	177	+10.4	-23.4*	198	+8.34	-10.6
	100 mg tid				187	+2.98	-15.9
60 minute postprandial plasma glucose (mg/dl)							
Placebo	266	+23.9		314	+14.8		
Miglitol	50 mg tid	261	-39.1	-63.0*	310	-51.6	-66.4*
	100 mg tid				296	-59.4	-74.2*
Fasting serum insulin (μU/ml)							
Placebo	16.11	+0.02		11.3	-0.83		
Miglitol	50 mg tid	16.11	-0.47	-0.49	12.6	-0.43	+0.4
	100 mg tid				16.7	-4.22	-3.4
60 minute postprandial insulin (μU/ml)							
Placebo	59.5	-6.00		37.1	+0.45		
Miglitol	50 mg tid	52.1	-13.5	-7.50*	38.7	-9.3	-9.8*
	100 mg tid				47.0	-13.9	-14.4*

* p<0.05 for difference from placebo (zero)

three non-US pivotal studies of monotherapy are shown in the following tables..
 was a 24 week dose-response study at 25, 50, 100, and 200 mg tid vs placebo. As shown in the table a dose-dependent reduction was observed for HbA1c, fasting and postprandial glucose and postprandial insulin. At 200 mg tid, there was a reduction of 1.02 units for hemoglobin A1c and 34.8 mg/dl fasting glucose for patients who completed the study. But 40 of the original 86 patients at 200 mg tid dropped out because of adverse events (as discussed in detail later this dosage exceeds the maximum recommended dose of 100 mg tid). The results from studies 0288 and 307 confirm that miglitol at 100 mg tid significantly lowered HbA1c, and fasting and 1 hr postprandial glucose. It had roughly the same (or slightly more) effect as acarbose 100 mg tid and had somewhat less effect than glibenclamide.

Non-US Adequate and Well-Controlled Studies Monotherapy in NIDDM Patients

(Study#) Country	Duration of Treatment	Treatment Group*	Number of Patients†				Male (%)	Caucasians. (%)	Mean Age (yr)	Mean BMI (Kg/m ²)	Mean Duration of NIDDM (years)
			R	V	DC						
					AE	LE					
(0281) NL	24 weeks	Placebo	94	76	2	8	59	89	63	27	4.3
		Miglitol 25 mg	93	74	6	2	53	91	64	27	5.2
		Miglitol 50 mg	93	77	4	7	57	94	63	27	6.0
		Miglitol 100 mg	95	56	22	4	54	95	63	28	5.0
		Miglitol 200 mg	93	46	40	2	70	94	64	27	5.3
(0288) O.CH, CR	24 weeks	Placebo	148	106	9	NR	40	100	62	27	3.6
		Miglitol 50 mg	148	119	8	NR	52	100	60	27	4.0
		Miglitol 100 mg	154	111	12	NR	56	100	61	28	4.2
		Acarbose 100 mg	156	114	17	NR	54	100	60	27	3.9
(0307) A, CR, D, IL	24 weeks	Placebo	65	42	1	4	57	100	59	29	3.9
		Miglitol 100 mg	67	40	3	1	55	100	61	29	4.8
		Glibenclamide	69	37	2	0	62	100	56	29	4.9

* Dosages of miglitol and of acarbose tid

† R= randomized; V= valid for efficacy; DC= discontinuations. AE = due to adverse events; LE = due to lack of efficacy
 NR = not recorded

Non-US Adequate and Well-Controlled Trials
 Monotherapy in NIDDM Patients
 Mean HbA_{1c}, Plasma Glucose and Serum Insulin

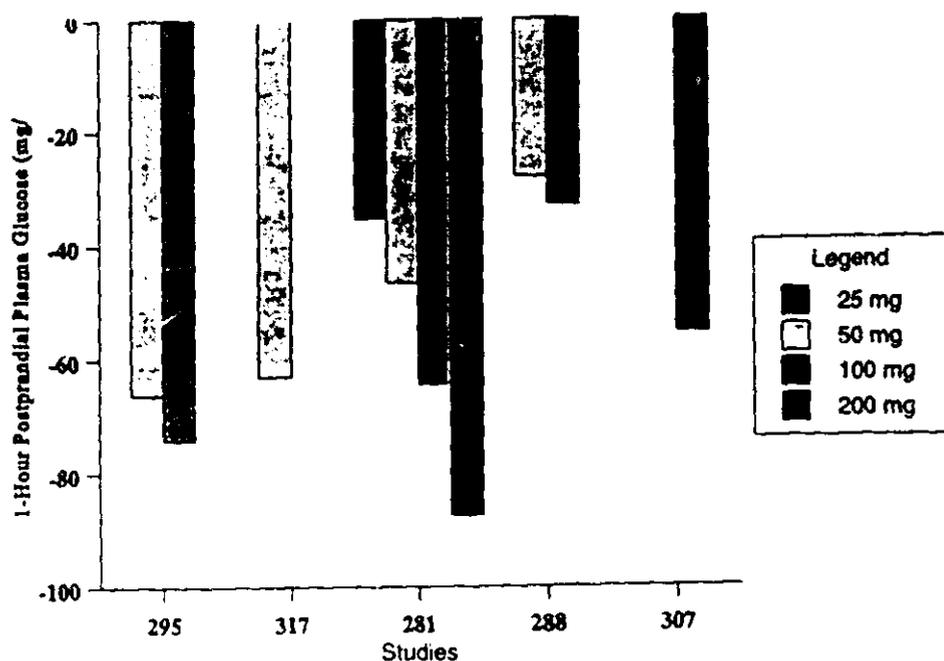
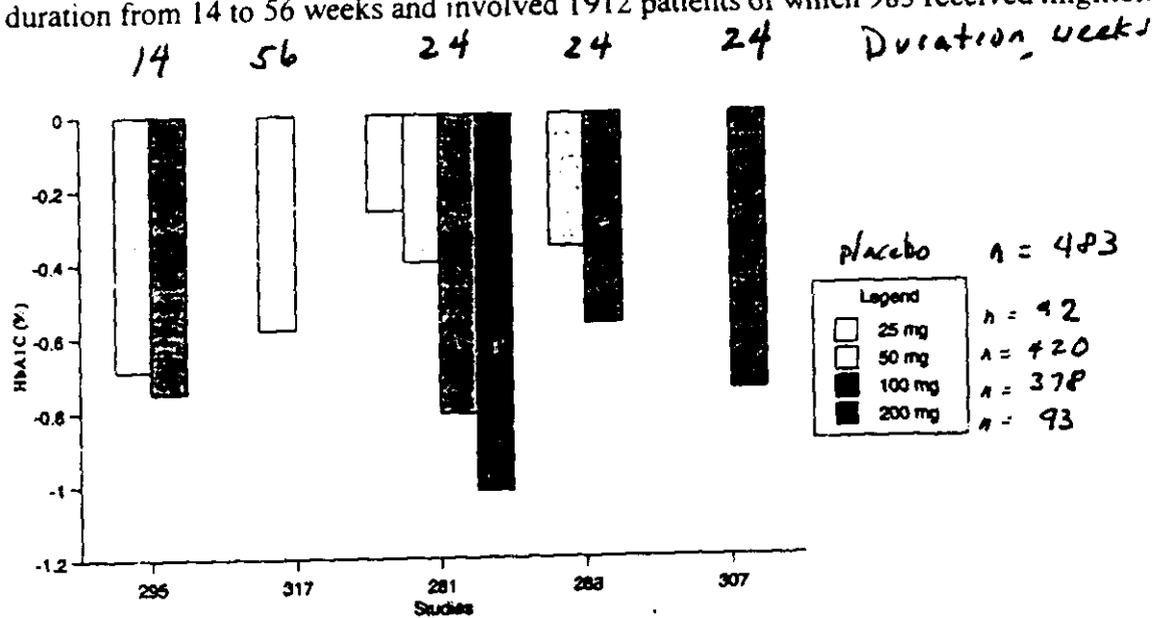
Study	0281			0288†			0307			
	Baseline	Change	Treatment Effect	Baseline	Change	Treatment Effect	Baseline	Change	Treatment Effect	
HbA_{1c} (%)										
Placebo	7.86	+ 0.18		7.60	+0.01		8.25	+0.32		
Miglitol	25 mg	8.15	- 0.08	- 0.26						
	50 mg	8.06	- 0.22	- 0.40	7.54	-0.35	-0.36*			
	100 mg	7.84	- 0.63	- 0.81*	7.57	-0.57	-0.57*	7.95	-0.43	-0.75*
	200 mg	8.09	- 0.84	- 1.02*						
Fasting plasma glucose (mg/dl)										
Placebo	185	+7.23		167	+7.60		177	+18.1		
Miglitol	25 mg	193	-0.65	-7.88						
	50 mg	192	-0.31	-7.54	168	-1.46	-9.06			
	100 mg	196	-13.4	-20.6*	165	-3.79	-11.4*	174	-10.0	-28.2*
	200 mg	202	-27.6	-34.8*						
60 minute postprandial plasma glucose (mg/dl)										
Placebo	270	+2.12		221	+7.88		253	+17.0		
Miglitol	25 mg	276	-33.3	-35.4*						
	50 mg	276	-44.5	-46.6*	221	-20.1	-28.0*			
	100 mg	260	-62.3	-64.4*	214	-25.0	-32.9*	241	-38.3	-55.3*
	200 mg	284	-85.4	-87.6*						
Fasting serum insulin (μU/ml)										
Placebo	17.9	-1.30					18.7	+0.21		
Miglitol	25 mg	16.9	-0.96	+0.34						
	50 mg	13.8	-2.52	-1.22						
	100 mg	16.1	-0.36	+0.93			17.7	+0.71	+0.50	
	200 mg	14.9	-1.99	-0.69						
60 minute postprandial insulin (μU/ml)										
Placebo	39.1	-1.65					47.6	-1.26		
Miglitol	25 mg	36.0	-8.01	-6.36*						
	50 mg	30.2	-10.0	-8.38*						
	100 mg	36.5	-10.1	-8.46*			47.8	-8.03	-6.77	
	200 mg	31.6	-11.8	-10.1*						

* p ≤ 0.05 for difference from placebo (zero)

† Population for pooling purposes

Results of two short (2 week) non-pivotal studies, D83-077 and D83-113 confirm reductions in fasting and 1 hour postprandial glucose, but HbA1c could not be determined.

Figures 1 and 2 show data from the five pivotal studies on the effects of miglitol on HbA1c and 1 hr postprandial glucose respectively. As I have added to the figures, these studies ranged in duration from 14 to 56 weeks and involved 1912 patients of which 983 received miglitol.



Effect of Miglitol in Patients on High Dose Sulfonylureas (SFU)

There are three pivotal studies in which miglitol was added to NIDDM patients maintained on a constant near maximal dose of SFU. These studies were done to investigate the value of the addition of miglitol to patients who cannot be adequately controlled on SFU alone. The results of studies D87-057 and D 92- 006 are shown in the following tables. Both studies demonstrate significant reductions of HbA1c, postprandial glucose and postprandial insulin levels. A dose-response relationship was seen in study D92-006 but not D87-057, perhaps because the latter study was only 14 weeks long , compared to the former which was 52 weeks long. A statistically significant reduction in fasting glucose was observed in D92-006, but a reduction was not statistically significant in D87-057.

US Adequate and Well-Controlled Studies Combination Therapy as Add-on in NIDDM patients on diet plus SFU

US # (Int. #) Country	Duration of Treatment	Treatment Group*	Number of Patients†				Male (%)	Cauca- sians (%)	Mean Age (yr)	Mean BMI (Kg/m ²)	Mean Duration of NIDDM (yr)
			R	V	DC						
					AE	LE					
D87-057 (0296) US	14 weeks	placebo	63	56	0	2	48	66	59	31	8.0
		miglitol 50 mg tid	81	57	3	0	67	63	58	31	9.7
		miglitol 100 mg tid	68	58	10	0	55	60	58	30	8.2
D92-006 (0314) US	52 weeks	placebo	118	115	7	12	56	81	59	30	7.5
		miglitol 25 mg tid	109	104	9	12	53	86	59	31	8.8
		miglitol 50 mg tid	113	104	8	6	61	84	59	31	8.7
		miglitol 100 mg tid	116	100	24	3	59	81	58	33	7.4

* Dosages for miglitol tid

† R = randomized (valid for safety); V = valid for efficacy, DC = discontinuations;
AE = due to adverse events; LE = due to lack of efficacy

US Adequate and Well-Controlled Studies
 Combination Therapy as Add-on in NIDDM Patients on Diet plus SFU
 Mean HbA_{1c}, Plasma Glucose and Insulin

Study	D87-057 (0296)			D92-006 (0314)			
	Baseline	Change	Treatment Effect	Baseline	Change	Treatment Effect	
HbA_{1c} (%)							
Placebo	8.87	+ 0.33		8.56	1.01		
Migliitol	25 mg			8.71	0.71	-0.30	
	50 mg	8.76	- 0.49	-0.82*	8.60	0.39	-0.62*
	100 mg	8.91	- 0.41	-0.74*	8.68	0.28	-0.73*
Fasting plasma glucose (mg/dl)							
Placebo	203	+ 6.82		196	40.3		
Migliitol	25 mg			204	30.4	-9.92	
	50 mg	196	- 9.88	- 16.7	198	24.4	-15.9*
	100 mg	204	-1.91	- 8.73	204	21.2	-19.1*
60 minute postprandial plasma glucose (mg/dl)							
Placebo	324	- 1.25		297	48.4		
Migliitol	25 mg			304	-1.98	-50.3*	
	50 mg	317	-69.4	-68.2*	300	-13.1	-61.5*
	100 mg	329	-72.8	-71.5*	308	-33.2	-81.6*
Fasting serum insulin (μU/ml)							
Placebo	11.6	+ 1.86		18.4	-1.53		
Migliitol	25 mg			18.4	0.38	+1.91	
	50 mg	10.9	-0.30	-2.16	20.2	-0.73	+0.80
	100 mg	13.3	-0.23	-2.09	20.4	-2.01	-0.48
60 minute postprandial insulin (μU/ml)							
Placebo	30.6	+0.77		40.9	-5.29		
Migliitol	25 mg			43.2	-9.86	-4.57	
	50 mg	28.1	-6.46	-7.23*	47.1	-14.5	-9.25*
	100 mg	31.5	-9.34	-10.1*	43.4	-14.2	-8.91*

* p ≤ 0.05

Study 0306 was performed in patients on an average dose of 10.5 mg glibenclamide. This 24 week study confirmed that miglitol 100 mg tid resulted in significant reduction of HbA1c (0.65 units vs placebo), fasting plasma glucose (28.3 mg/dl) and 1 hr postprandial glucose (46.5 mg/dl). Insulin levels were lower with miglitol but the difference was not statistically significant. The mean weight difference was 4.4 kg in patients on miglitol compared to those on SFU alone.

Effects of Miglitol in the Elderly

Study 272 was a 16 week study conducted in Finland in which miglitol 100 mg tid was added to SFU. The results in young patients (30-60 , n=13 placebo, n= 12 miglitol) and old patients (65-80, n = 22 placebo, n = 19 miglitol) were analyzed separately. As shown in the table, the reduction of HbA1c and fasting and postprandial glucose levels were much greater in older patients than in younger patients. The mean reduction of 0.86 % units for HbA1c in all patients (younger and older) is similar to what had been observed in other studies already discussed. But the 1.54% unit reduction of HbA1c in older patients on miglitol is the most reported in any study. Postprandial glucose rose in the placebo patients but fell in the miglitol patients. As shown in the figure, the effect of miglitol on postprandial glucose was also greater in the older patients than in the younger patients.

As has been true in all other studies, miglitol patients had more AE's, primarily gastrointestinal, than placebo patients. Adverse events occurred in 80% of younger patients on miglitol and 76.7% of older patients on miglitol. This compares to 42.1% of younger patients on placebo and 45.2 % of older patients. For miglitol patients, drop-outs due to AE's occurred in 10% of younger patients and 20% of older patients. For placebo this was 3.2% in younger patients and 6.5% in older patients. One of the older placebo patients died. There were no deaths in the miglitol patients.

Combination Therapy in NIDDM Patients on Diet plus SFU

Study# Country	Duration of Treatment*	Treatment Group*	Number of Patients†				Male (%)	Cauca- sians (%)
			R	V	DC			
					AE	LE		
0272 Finland	16 weeks	Placebo	50	35	3	NR	43	100
		Age 30-60	19	13	1	NR		
		Age 65-80	31	22	2	NR		
		Miglitol 100 mg	50	31	8	NR	39	100
		Age 30-60	20	12	2	NR		
		Age 65-80	30	19	6	NR		

* Dosages of miglitol tid
 † R= randomized; V= valid for efficacy; DC= discontinuations; AE = due to adverse events;
 LE = due to lack of efficacy.
 NR = not recorded

	All Patients			Age 30-60			Age 65-80		
	Baseline	Change	Treat- ment Effect	Baseline	Change	Treat- ment Effect	Baseline	Change	Treat- ment Effect
HbA_{1c} (%)									
Placebo	10.48	+0.22		10.85	-0.13		10.38	+0.56	
Miglitol 100 mg	10.71	-0.64	-0.86*	10.27	-0.31	-0.18	10.98	-0.98	-1.54*
Fasting plasma glucose (mg/dl)									
Placebo	193	+14.4		200	+8.84		189	+20.0	
Miglitol 100 mg	196	-6.84	-21.2	199	-6.84	-15.5	195	-7.02	-27.0*
80 minute postprandial plasma glucose (mg/dl)									
Placebo	279	+6.48		277	+2.52		280	+10.4	
Miglitol 100 mg	289	-47.3	-53.8*	296	-39.8	-42.3*	285	-54.7	-65.2*

* p ≤ 0.05
 † = normal value 6.0% to 8.0%

Effects of Miglitol in Patients on Insulin:

There are two 24 week studies of addition of 100 mg tid miglitol to insulin in NIDDM patients already receiving insulin. Study 0273, conducted in Greece, showed mean reduction in HbA1c of 1.3 % units vs placebo and a fall in one hour plasma glucose of 61 mg/dl. This result was not confirmed; however, in study 0274 conducted in the Czech Republic. There are also two small 2 week studies in patients with IDDM. One study showed a significant reduction in 1 hr postprandial glucose in patients on miglitol 50 mg tid vs placebo. The other study used 25 mg tid miglitol and the observed reduction in postprandial glucose was not statistically significant.

Mixed Patient Groups

There are two foreign studies in which miglitol was added to either diet alone or SFU in NIDDM patients. Study 0278, conducted in Britain consisted of three treatment arms, miglitol 50 mg tid, 100 mg tid and placebo, approximately 100 patients in each group and lasted six months. Study 0283, conducted in Spain compared miglitol 100 mg tid to placebo and lasted 18 weeks. In both studies, patients on miglitol 100 mg tid demonstrated a fall in HbA1c of about 0.75 % units. Patients on 50 mg tid had a mean reduction of 0.35 % units.

Comparisons of Miglitol to other Treatment:

Comparisons between miglitol 100 mg tid and metformin 850 mg bid were made in study 0264 and between miglitol 100 mg tid and glibenclamide 5 mg bid were made in study 0277 (see tables). Unfortunately, neither study had a placebo arm so that no definite effect of miglitol as monotherapy relative to placebo could be ascertained. In study 0264 miglitol 100 mg tid was significantly less effective in lowering HbA1c and fasting glucose than metformin but was more effective than metformin in lowering postprandial glucose and insulin. Study 0277 showed that glibenclamide was somewhat more effective in lowering HbA1c; however, miglitol was more effective in lowering postprandial glucose. Insulin levels were reduced by miglitol but increased

by glibenclamide.

Int. # Country	Duration of Treatment	Treatment Group*	Number of Patients†				Male (%)	Cauca- sians (%)	Mean Age (yr)	Mean BMI (Kg/m ²)	Mean Duration of NIDDM (yr)
			R	V	DC AE	LE					
0264 France	24 weeks	miglitol 100mg metformin 850mg bid	90	76	16	NR	59	NR	54	NR	6.1
			88	76	10	NR	53	NR	55	NR	6.9
0277 Italy	24 weeks	miglitol 100mg glibenclamide 5mg bid	52	49	1	NR	65	100	57	27	5.0
			48	47	0	NR	50	100	59	27	7.0

* Dosages of miglitol tid

† R = randomized; V = valid for efficacy; DC = discontinuations; AE = due to adverse events;

LE = due to lack of efficacy

NR = not recorded

Study		0264			0277		
		Baseline	Endpoint	Change	Baseline	Endpoint	Change
HbA_{1c} (%)							
Miglitol	100 mg tid	7.02	6.88	-0.14	8.07	7.29	-0.78*
Glibenclamide	5 mg bid				7.93	6.75	-1.18*
Metformin	850 mg bid	6.99	6.30	-0.69			
Fasting plasma glucose (mg/dl)							
Miglitol	100 mg tid	204	204	0	156	142	-13.5
Glibenclamide	5 mg bid				146	134	-12.6
Metformin	850 mg bid	203	180	-23.2			
60-minute postprandial plasma glucose (mg/dl)							
Miglitol	100 mg tid	285	246	-39.1	239	205	-34.3
Glibenclamide	5 mg bid				234	231	-2.4
Metformin	850 mg bid	279	250	-29.5			
Fasting serum insulin (μU/ml)							
Miglitol	100 mg tid	18.7	17.5	-1.22	24.3	23.1	-1.17
Glibenclamide	5 mg bid				24.1	29.1	+5.07
Metformin	850 mg bid	18.7	18.4	-0.29			
60-minute postprandial insulin (μU/ml)							
Miglitol	100 mg tid	56.3	40.0	-16.3	61.5	54.4	-7.06
Glibenclamide	5 mg bid				70.7	74.2	+3.49
Metformin	850 mg bid	54.6	52.6	-1.98			

* p<0.05 for difference from baseline (testing for significance done only for HbA_{1c} in Study 0277).

Study 306 described previously also included a metformin arm in which 850 mg bid metformin was added to patients on glibenclamide (10.5 mg average). As shown in the following table, the fall of HbA1c in patients treated with metformin (1.56 % units vs placebo) was greater than that with miglitol 100 mg tid (0.65 %units). The reduction of fasting glucose was also greater with metformin (54.9 mg/dl) than with miglitol (28.3 mg/dl).

**Non-US Adequate and Well-Controlled studies
Combination Therapy in NIDDM Patients on Diet plus SFU**

Study# Country	Duration of Treatment	Treatment Group*	Number of Patients†				Male (%)	Cauca- sians (%)	Mean Age (yr)	Mean BMI (Kg/m ²)	Mean Duration of NIDDM (years)
			R	V	DC AE LE						
0306	24 weeks	placebo	58	43	1	2	47	100	60	29	8.0
A,CR,		miglitol 100 mg	58	48	3	0	40	100	60	30	7.3
D,GR		metformin 850 mg	58	49	2	1	49	100	60	30	9.2

* Dosages of miglitol tid and metformin bid
† R= randomized; V= valid for efficacy; DC= discontinuations; AE = due to adverse events; LE = due to lack of efficacy.

Study	0306		
	Baseline	Change	Treatment Effect
HbA1c (%)			
Placebo	9.16	+0.16	
Miglitol 100 mg	9.11	-0.50	-0.65*
Fasting plasma glucose (mg/dl)			
Placebo	199	+9.90	
Miglitol 100 mg	214	-18.4	-28.3*
60 minute postprandial plasma glucose (mg/dl)			
Placebo	268	+10.4	
Miglitol 100 mg	289	-36.1	-46.5*
Fasting serum insulin (µU/ml)			
Placebo	21.6	-2.67	
Miglitol 100 mg	22.5	-4.80	-2.13
60 minute postprandial insulin (µU/ml)			
Placebo	43.1	-7.80	
Miglitol 100 mg	38.2	-11.6	-3.78

One additional study, D92-009, used low dose SFU (glyburide 2.5 mg bid) both alone and in combination with miglitol, 50 mg tid in patients who were previously on diet alone. Under these conditions the use of miglitol lowered the 1 hour postprandial glucose and insulin in comparison to SFU alone but had little impact on HbA1c. Glyburide alone was also more effective than miglitol alone, but miglitol blocked the weight promoting effect of glyburide. (see tables)

US # (Int. #) Country	Duration of Treatment	Treatment Group*	Number of Patients†				Male (%)	Caucasians (%)	Mean Age (yr)	Mean BMI (Kg/m ²)	Mean Duration of NIDDM (yr)
			R	V	DC						
					AE	LE					
D92-009 (0317) US	52 weeks	placebo	108	98	10	17	63	80	56	32	4.5
		miglitol 50 mg tid	113	104	13	6	52	76	55	31	3.6
		glyburide 2.5 mg tid	109	99	14	4	62	78	54	32	4.5
		miglitol & glyburide	112	103	20	0	49	86	56	32	4.1

* Dosages for miglitol tid

† R = randomized (valid for safety); V = valid for efficacy; DC = discontinuations; AE = due to adverse events; LE = due to lack of efficacy

	Baseline	Change	Treatment Effect
HbA1c (%)			
Placebo + SFU 2.5 mg bid	8.00	-0.65	
Miglitol 50 mg tid + SFU 2.5 mg bid.	7.96	-0.81	-0.16
Fasting plasma glucose (mg/dl)			
Placebo + SFU 2.5 mg bid	179	-20.7	
Miglitol 50 mg tid + SFU 2.5 mg bid	184	-22.3	-1.57
60 minute postprandial plasma glucose (mg/dl)			
Placebo + SFU 2.5 mg bid	265	-10.2	
Miglitol 50 mg tid + SFU 2.5 mg bid	281	-65.4	-55.2*
Fasting serum insulin (μU/ml)			
Placebo + SFU 2.5 mg bid	15.2	4.54	
Miglitol 50 mg tid + SFU 2.5 mg bid	15.6	2.89	-1.65
60 minute postprandial insulin (μU/ml)			
Placebo + SFU 2.5 mg bid	48.3	11.76	
Miglitol 50 mg tid + SFU 2.5 mg bid	53.1	-9.13	-20.9*

* p ≤ 0.05

Other Results:

No significant differences were observed between men and women or between Caucasians, Blacks and Hispanics with respect to response to miglitol. Elderly patients (65-80) demonstrated a significantly better response to treatment than did younger patients (30-60) in study 272. Body mass index and duration of NIDDM did not affect the response to treatment. Patients whose starting HbA1c was above the median had a greater response (0.68 % units) to miglitol than patients below the median (0.44 % units).

A small reduction in body weight attributable to miglitol was observed in some studies but not others. Miglitol also appeared to block the weight promoting effect of SFU in some studies but not others. There was no effect on fasting lipid levels but postprandial triglyceride levels were lowered on miglitol. A decrease in urinary albumin excretion was observed in the two one-year US studies D 92-006 and D 92-009.

Study D92-037 utilized a euglycemic insulin clamp in NIDDM patients and demonstrated that miglitol had no effect on insulin sensitivity or hepatic glucose production either in the basal state or after exercise. This study shows that miglitol does not affect glucose metabolism itself and therefore does not have the potential to cause hypoglycemia when used alone

D92-036 was a study done by Dr Colwell of the University of South Carolina to evaluate the effects of miglitol on some of the abnormalities of clotting and fibrinolytic factors known to be abnormally high in patients with diabetes. Two weeks of therapy was associated with a statistically significant reduction in factor V11 activity. This was felt to represent a possible benefit in view of the association between the elevated levels of factor V11 in NIDDM and the increased risk of vascular disease. Small reductions in tissue plasminogen activator (tap) and plasminogen activator inhibitor-1 (PAI-1) were observed but the changes were not statistically significant. No other changes in clotting or fibrinolytic factors were observed.

SAFETY

Studies in the US

Adverse events

There are 906 NIDDM patients in placebo- controlled US trials. 85% of these patients received 150-300 mg per day. 27% (n= 246) received the maximum recommended dose of 300 mg per day. Of these 246 patients, 69 patients(32%) received miglitol 300 mg per day for over 48 weeks, and 208(85 %) received this dose for over 12 weeks. In comparison to placebo there was increased reporting of adverse events involving the gastrointestinal system(62.3% vs 36.0 % $p<0.001$) in miglitol treated patients, increased reporting of rash (4.3% vs 2.4% $p=0.016$) and decreased reporting in the respiratory system (30.4 vs 36.9% $p=0.003$). 20 of the 39 rashes in patients on miglitol were attributed to specific etiologies not related to the drug (insect bite, poison ivy, etc). 25 of 39 were judged by investigators to have no relation to miglitol and 8 of the remaining 14 were judged to have a "remote" relation to the drug. There is no explanation for the decreased reporting in the respiratory system(reports of rhinitis were less frequent in patients on miglitol than placebo). A breakdown of the gastrointestinal events is shown in the table:

Gastrointestinal Events in US Placebo-Controlled Trials

adverse event	placebo	miglitol	P-value
any GI event	196/545(36.0)	564/906 (62.3%)	<0.001
abdomen enlarged	0	10/906 (1.1%)	0.017
flatulence	70/543 (12.9%)	387/901 (43.0%)	<0.001
diarrhea	50/545 (11.0%)	268/906 (29.6%)	<0.001
dyspepsia	17/545 (3.1%)	52/904 (5.8%)	0.036
rectal disorder	0	8/906 (0.9%)	0.028

These gastrointestinal events are predictable consequences of miglitol's primary action which increases the amount of undigested carbohydrate in the lower bowel. The "rectal disorder" pertained to hemorrhoids which were exacerbated by increased stool volume produced by miglitol. Abdominal pain, diarrhea and flatulence were clearly dose related. Flatulence and diarrhea occurred more frequently in older patients than in younger patients. For patient over 65, 39% (miglitol minus placebo) reported flatulence and 25 % reported diarrhea. For patients under 40, 15%(miglitol minus placebo) reported flatulence and 10 % reported diarrhea. Flatulence and diarrhea were also somewhat more frequent in Caucasians than in Blacks or Hispanics.

Despite the high incidence of gastrointestinal complaints, only 11.6 % of patients on miglitol and 7.0% of patients on placebo left the studies because of adverse events ($p=0.003$). Among the miglitol-treated patients reasons for discontinuing study medication were abdominal pain (3%), flatulence (6%), and diarrhea (5%). Less than 1% of placebo-treated patients discontinued study medication for any of these reasons. 4% of patients on miglitol and 7 % of patients on placebo left the studies because of insufficient therapeutic effect($p=0.001$). Overall completion rate was 78% for miglitol and 77% for placebo.

Deaths:

There were three deaths in the US studies, two with miglitol and one with placebo. One miglitol-treated patient was a 77 year old women who died of a stroke following an acute myocardial infarction. The second miglitol treated patient was an 83 year old man who died of large cell lymphoma. The study drug was stopped 12 days after the diagnosis was made. The patient died three months later. The placebo-treated patient was a 71 year old man who fell at home 4 days after being randomized. He was found to have a large subarachnoid hemorrhage and died two days later.

EKG:

It was initially reported that 11 miglitol patients developed low voltage QRS and 10 developed first degree AV block. No placebo treated patients were reported to have similar EKG changes. Investigators were asked to reread the baseline and endpoint tracings and all of them reported that there had been no change in the EKG's with treatment. The discrepancy was apparently due to the fact that different physicians had read the EKG's or that computer printouts were used. In response to a request of April, 11 1996, the Sponsor submitted the copies of the original EKG tracings on May 8. Review of these tracings supports the Sponsor's contention that the changes were spurious. An example of two EKG's on the same patient before and during therapy is appended: The first tracing has a rate of 62, PR interval of 208 msec and was read as " normal sinus rhythm, normal ECG". The second tracing has a rate of 57, PR interval of 224 and was read as " sinus bradycardia with 1st degree AV block, abnormal ECG". However, the two tracings when viewed side by side are nearly identical.

D 92-006
1900.3
V.S. 4

Revised by [Signature]

25ms/s
10mm/mV
100Hz
Pgm 108B
12SLtm v78
C

Med: None
72yr
Sex: M Race: Cauc
Loc: 3E Room: M12
Option: 0

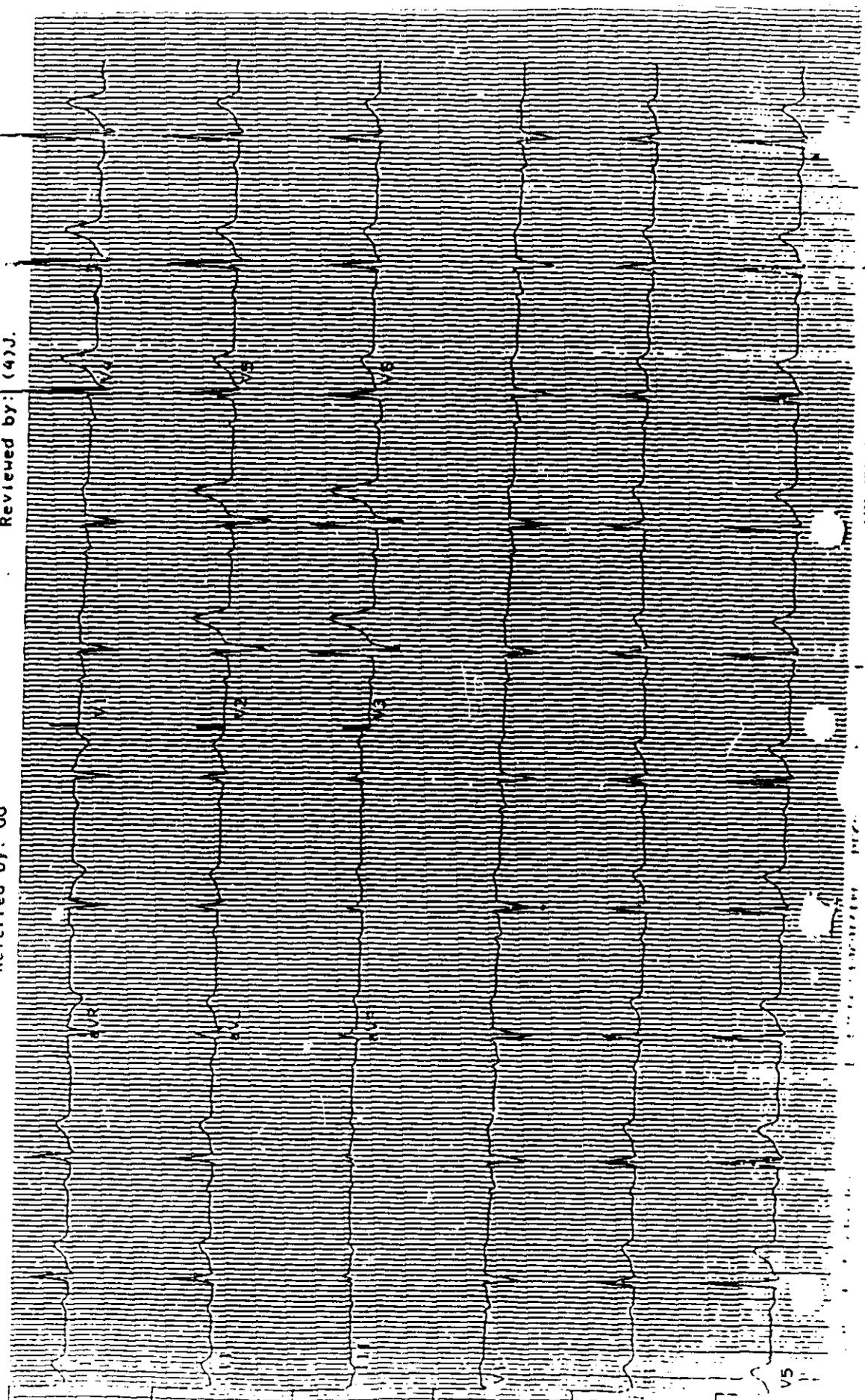
Vent. rate 62 BPM
PR interval 208 ms
QRS duration 112 ms
QT/QTc 396/402 ms

Cart: I P-R-T axes II 3I 2I

NORMAL SINUS RHYTHM
NORMAL ECG
DONE AT P16

Referred by: 00

Reviewed by: (4)J.



P19 ROUTINE F

12-JUL-1994 11:30

D92-004
19003
VS 13

SINUS BRADYCARDIA WITH 1ST DEGREE AV BLOCK
• ABNORMAL ECG
DONE AT P16 ✓

ID: 021865073
57 BPM
224 ms
116 ms
396/385 ms
7 22 18

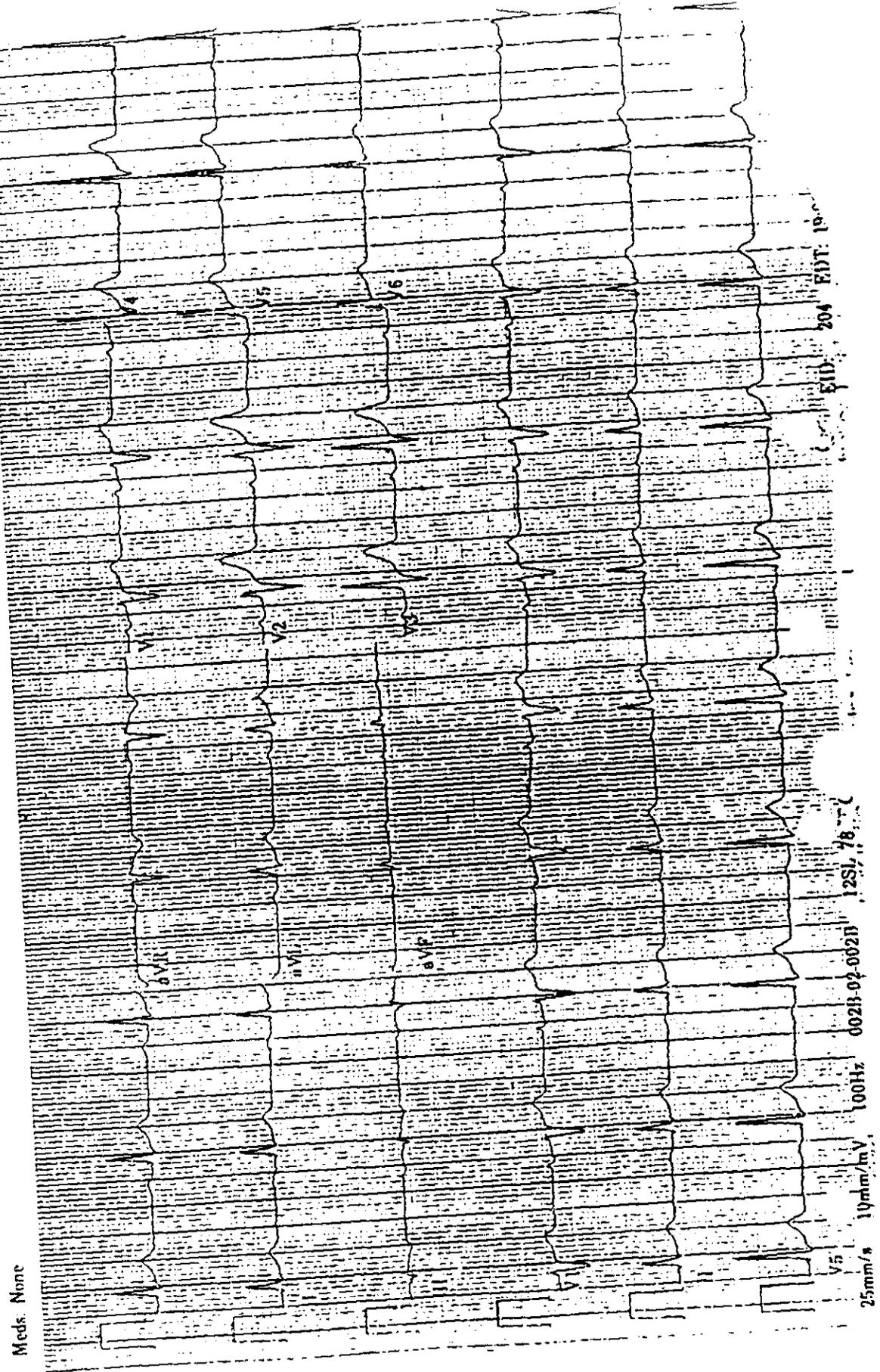
Vent. rate
PR interval
QRS duration
QT/QTc
P-R-T axes

73 yr
Male
Caucasian
01b
Room: P19
Loc: 38 Opt: 0

Technician ID: 0

Referred by: HOOGWERT

Confirmed by:



Meds: None

204 EDT 1994

002H-02-002H 12SL 78

100Hz
25mm/s 10mm/mV
V5

Clinical chemistry:

Special attention was paid to liver function tests in view of the dose-related rise in transaminases which occurred with acarbose. However, there was no difference in the incidence of elevated liver function tests between patients on miglitol and patients on placebo. Indeed, elevated SGOT levels occurred in 4% of patients on miglitol and 5% of patients on placebo. An elevated SGPT occurred in 6% of patient on miglitol and 7 % of patient on placebo. Incidence of elevation of alkaline phosphatase, total bilirubin and LDH were exactly the same in both groups. An elevation of any of these liver function tests to 3x normal occurred in 2/906 miglitol treated patients (0.22%) and 3/545 (0.55%) placebo patients.

There appeared to be an increased incidence of elevated fibrinogen levels at endpoint in miglitol-treated (21.3%) vs placebo treated patients(13.8%, P=0.12). This difference was not dose related. To the contrary it occurred about twice as often in patients on 25 mg tid as in patients on 100 mg tid. In many cases, the elevation which occurred at six months of treatment resolved by the end of one year. It is not clear what clinical significance, if any, results from this rise in fibrinogen.

A low serum iron was observed in 4.2% of placebo-treated patients and 9.2% (p=0.021) of miglitol treated patients. The effect was not dose-dependent. To the contrary, odds ratio analysis was statistically significant only for 25 mg tid and not for the higher doses. The fall in serum iron was greatest in patients whose starting value was low. Serum iron was somewhat lower in the miglitol group at baseline than in placebo. Looking just at patients whose starting value was low, there was a fall in serum iron after six months of treatment in both miglitol and placebo treated patients which partly returned to normal by 12 months in both groups. Two other pieces of evidence point against the fall in serum iron having any clinical significance. The first is the absence of a difference between miglitol treated patients and controls with respect to hematocrit, hemoglobin or mean corpuscular volume. The second piece of evidence is lack of compensatory rise in total iron binding capacity in miglitol treated patients.

Safety Review of all US placebo controlled trials

The preceding safety data were based on 906 NIDDM patients, 81% of which received miglitol for 12 weeks or more. These results did not include the 50 IDDM patients who received the drug or the six NIDDM patients who received the drug as part of a two week cross over trial.

Inclusion of these patients (designated in the NDA as pool 2) does not substantially affect the safety data presented previously (pool 1) except for two transient episodes of high serum sodium which the Sponsor attributes to non-standardization of the laboratory. Since IDDM patients are not included in the proposed labeling, I do not believe that further use of "pool 2" data is necessary.

The Sponsor also reviewed safety data in patients in the two one year trials, studies D92-006 and D 92- 009 who were treated for over six months. This includes 465 patients on miglitol and 275 patients on placebo. Beyond six months of treatment there was no longer any difference between miglitol and placebo with respect to reporting of adverse events related to the gastrointestinal system. The dropout rate due to adverse events was 3% for miglitol and 1% for placebo beyond six months which was not statistically different. However, the dropout rate due to lack of efficacy after six months was significantly ($p=0.003$) greater with placebo(7%) than with miglitol (3%).

Safety Data from Studies outside the United States

There are safety data from foreign (non-US) studies since 1983 involving 3667 miglitol treated patients. Adverse events, primarily gastrointestinal, were reported in 2114 (57.6%). There were 2166 patients with NIDDM who received miglitol in placebo-controlled trials. More than 1300 of these patients received miglitol for more than 12 weeks and 929 received miglitol for more than 24 weeks. 262 patients (11%) dropped out due to adverse events or intercurrent illness while taking miglitol. There were six deaths (0.25%), none of which were attributed to the drug.

Of 1706 patients taking placebo, 69 (4%) dropped out due to adverse events and there were 8 deaths (0.5%). Adverse events occurred more frequently at 200 mg tid of miglitol than at the lower doses. The only consistent laboratory abnormality was low serum iron levels in miglitol-treated patients.

Of all the 3677 patients who received miglitol there were 16 deaths (0.43%), three attributed to myocardial infarction, two to heart failure, two to cerebrovascular accident. There were two patients with carcinoma of the pancreas, one suicide, one fatal gastrointestinal bleed and one case of pulmonary edema. In four cases the cause of death was not known or unstated. Among the placebo-treated patients, there were eight (0.45%) deaths two from myocardial infarction, one from stroke, one from cancer, one from perforated appendix, one from pneumonia, and one unknown.

Details of Pivotal Studies:

D92-009

Monotherapy and in Combination with Glyburide

This is a 56 week United States study designed to compare the effects of miglitol, glyburide, and a combination of Mig + Gly to placebo. Patients had NIDDM and had not been off oral agents for at least 6 months and insulin for at least 28 days. Patients who had been on insulin for 21 or more days in the proceeding six months were excluded. Patients were 30 years old or older and had HbA1c of 6.5-10.0%. An outline is shown below:

Weeks		-6	-2	0		2	4	8	16	24	32	40	48	56		
SCREENING	PLACEBO RUN IN	Placebo TID <i>n = 108 (initial) n = 76 (final)</i>														
		Miglitol 25 mg TID <i>n = 113</i>				Miglitol 50 mg TID <i>n = 83 (final)</i>										
		Glyburide 2.5 mg qAM <i>n = 109</i>				Glyburide 2.5 mg BID <i>n = 82 (final)</i>										
		Miglitol 25 mg TID and Glyburide 2.5 mg qAM <i>n = 112</i>				Miglitol 50 mg TID and Glyburide 2.5 mg BID <i>n = 89 (final)</i>										
Visit		0	1	2	3	4		5	6	7	8	9	10	11	12	13
Meal Test					X							X				X
HbA1c	X			X	X			X	X	X	X	X	X	X	X	X

Approximately one third of patients in each of the treatment groups failed to complete the study. There was no significant difference among the groups in the number of patients who dropped out, nor the reasons they dropped out, except that more patients in the placebo group dropped out because of lack of efficacy. As is shown below, a significant change at 56 weeks in HbA1c was seen in all three drug groups vs placebo. The treatment effect with miglitol alone (-0.58 % units) was significantly less than that seen with Glyburide alone (-1.36 % units). The combination of

the two drugs gave a greater difference than either alone (-1.52 % units) but the change was not statistically different from Glyburide alone. These results are essentially the same if shown at the last visit instead of at 56 weeks, except of course that the number of patients would be larger.

Treatment Group	Change from Baseline			Placebo-Subtracted Change from Baseline (Standard Error)	
	N	LS Mean	Standard Error		
Placebo	76	0.71 ABC	0.14		
Miglitol 50mg TID	83	0.13 BC	0.14	-0.58	(0.19)
Glyburide 2.5mg BID	82	-0.65	0.14	-1.36	(0.20)
Miglitol + Glyburide	89	-0.81	0.13	-1.52	(0.19)

- A: Significantly different from miglitol 50mg TID
- B: Significantly different from glyburide 2.5mg BID
- C: Significantly different from miglitol 50mg TID + glyburide 2.5mg BID

There was a greater drug effect (miglitol minus placebo) in patients older than 60 years old than in patients 60 years old and younger (-1.07 % units vs -0.28). Age did not affect the change in HbA1c in the other treatment groups. Also, the patients whose starting HbA1c was > 7.8 exhibited a greater reduction of HbA1c in all three treatment groups. Other significant differences after 56 weeks are reductions in postprandial glucose and triglycerides in all drug groups. Insulin levels rose in the glyburide group but fell in the miglitol group relative to baseline and was unchanged in the combination Mig + Gly group. Body weight fell in patients in the miglitol and placebo group but rose in patients in the Glyburide group. Addition of miglitol to glyburide partially ameliorated this rise in body weight.

Major adverse events in patients on miglitol were flatulence (31%) and diarrhea (17%). Hypoglycemia occurred in 40% of patients on Glyburide alone and 36% of patients on Miglitol + Gly compared to 5% of patients on miglitol alone and 9% of patients on placebo.

Study 0281

Dose-response relationship

This study was conducted in the Netherlands. It compared four treatment doses of miglitol, 25 mg tid, 50 mg tid, 100 mg tid, and 200 mg tid with placebo. There was a four week placebo run-in period followed by 24 weeks of treatment with active drug or placebo. The patients who received 100 mg tid and 200 mg tid, received half their dose for the first two weeks and the full dose thereafter. The patients had NIDDM for at least six months and were not taking any other antidiabetic medication. They had a minimal age of 40 years and a minimal fasting plasma glucose of 7.0 mM. HbA1c had to be in the range from 6.1 % to 10.4 %. Patients received a standard breakfast meal tolerance test consisting of 4 slices of bread with margarine, jam and cheese. The total caloric content of the breakfast was 372 Kcal, 49% carbohydrate, 40% fat, and 11% protein.

HbA1c was the primary measure of efficacy. Secondary measures of efficacy were plasma glucose and insulin levels. Results of the effect of miglitol on changes in HbA1c are shown in the tables. The 'p' value indicates comparison to placebo control. Both "intent to treat " and " per protocol" analyses are shown:

Intent to Treat

	placebo	25 mg tid	50 mg tid	100 mg tid	200 mg tid
n	87	84	84	71	58
baseline	7.94	8.14	8.09	8	8.1
endpoint	8.34	8.06	8.11	7.54	7.23
difference	0.4	-0.06	0.02	-0.46	-0.86
treatment eff		0.16	0.38	0.86	1.26
p value		0.0137	0.0169	0.0001	0.0001

per protocol correct

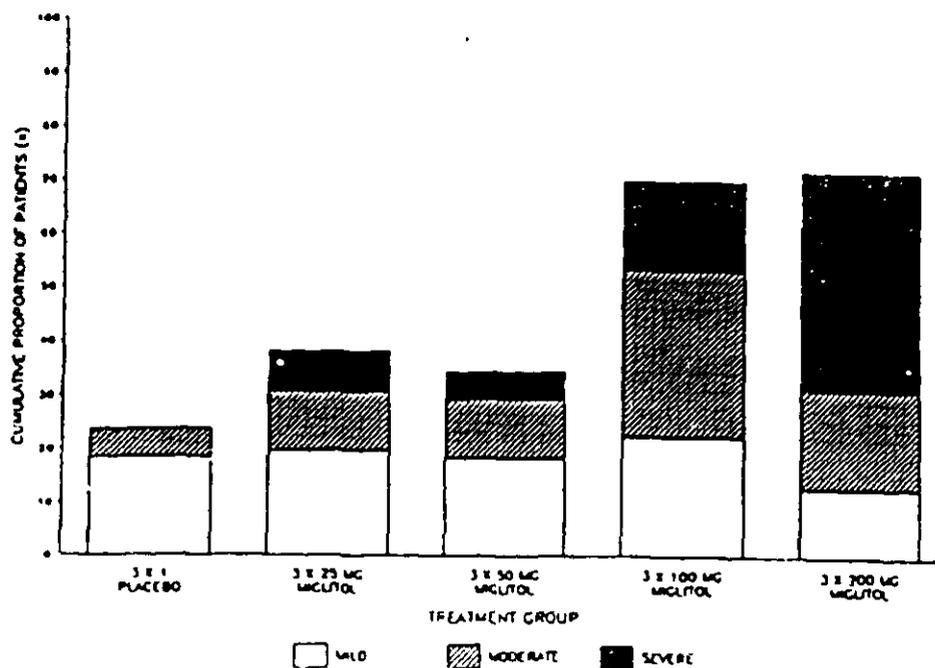
	placebo	25 mg tid	50 mg tid	100 mg tid	200 mg tid
n	76	74	77	56	46
baseline	7.86	8.15	8.06	7.84	8.09
endpoint	8.16	8.07	7.87	7.23	7.3
difference	0.29	-0.08	-0.18	-0.6	-0.78
treatment eff		0.37	0.47	0.89	1.07
p value		0.1449	0.0272	0.001	0.001

The falls of HbA1c were also associated with decreases relative to placebo in glucose and insulin levels. There were no changes in serum cholesterol levels and a small decrease in fasting triglyceride.

As shown in the table, there was a dose - dependent increase in gastrointestinal complaints in patients on miglitol:

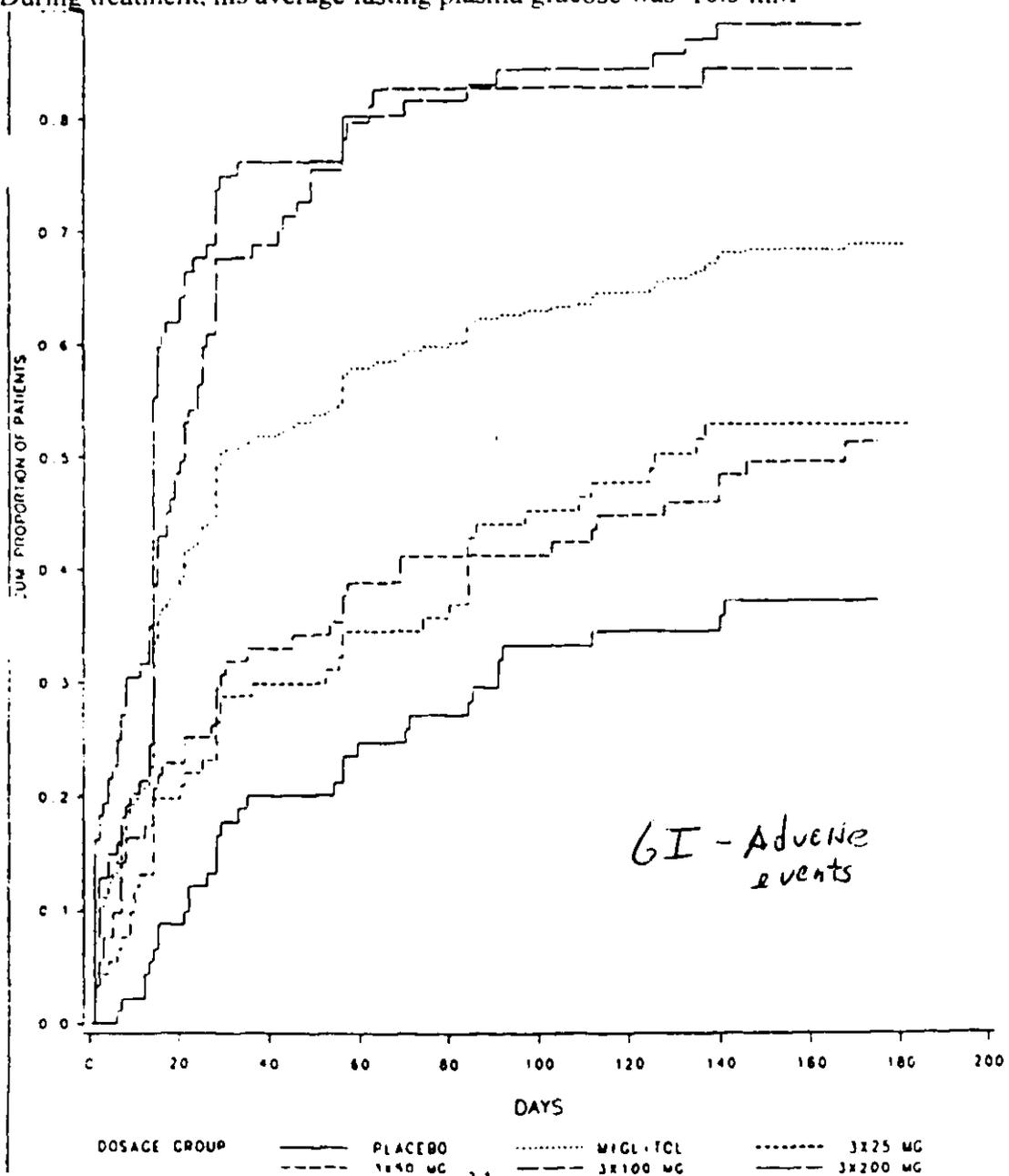
	placebo	25 mg tid	50 mg tid	100 mg tid	200 mg tid
flatulence. %	23.7	38	34.4	70.2	72
diarrhea. %	15.1	15.2	21.5	53.2	62.4
abdominal pain %	8.6	6.5	9.7	17	31.2

As shown in the figures, the severity of the complaints was also dose-dependent. Most of the patients who had gastrointestinal complaints on the two highest doses of miglitol developed those complaints within the first month of therapy. By contrast, there was a steady rise in gastrointestinal complaints throughout the six months of study in patients receiving placebo. There were no effects of miglitol seen on vital signs or clinical chemistry tests including liver enzymes.



incidence and severity of flatulence

121 patients (26%) dropped out of the study post-randomization. In 74 patients, the reason they dropped out was an adverse event. 40 of these patients were on miglitol 200 mg tid, 22 were on miglitol 100 mg tid and 2 were on placebo. By contrast, 23 patients dropped out because of lack of treatment effect (persistent hyperglycemia), 8 of these were on placebo, 4 on miglitol 100 mg tid and 2 on miglitol 200 mg tid. There were five deaths, four during the placebo run-in period and one while taking miglitol 100 mg tid. This last patient was a 71 year old male who died of an acute myocardial infarction with congestive heart failure after having been on miglitol for 14 weeks. During treatment, his average fasting plasma glucose was 10.5 mM



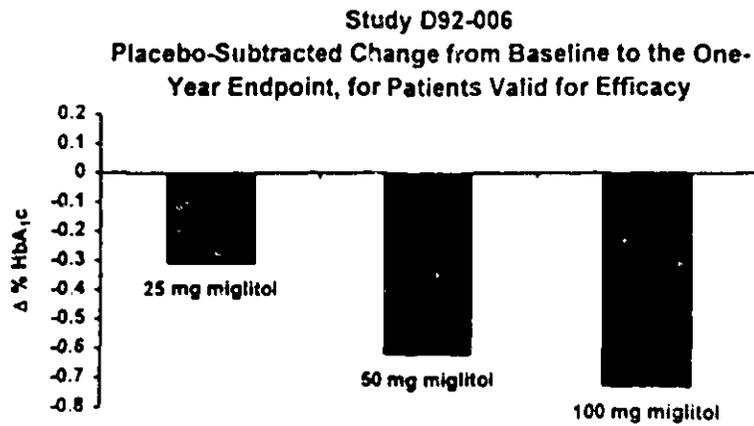
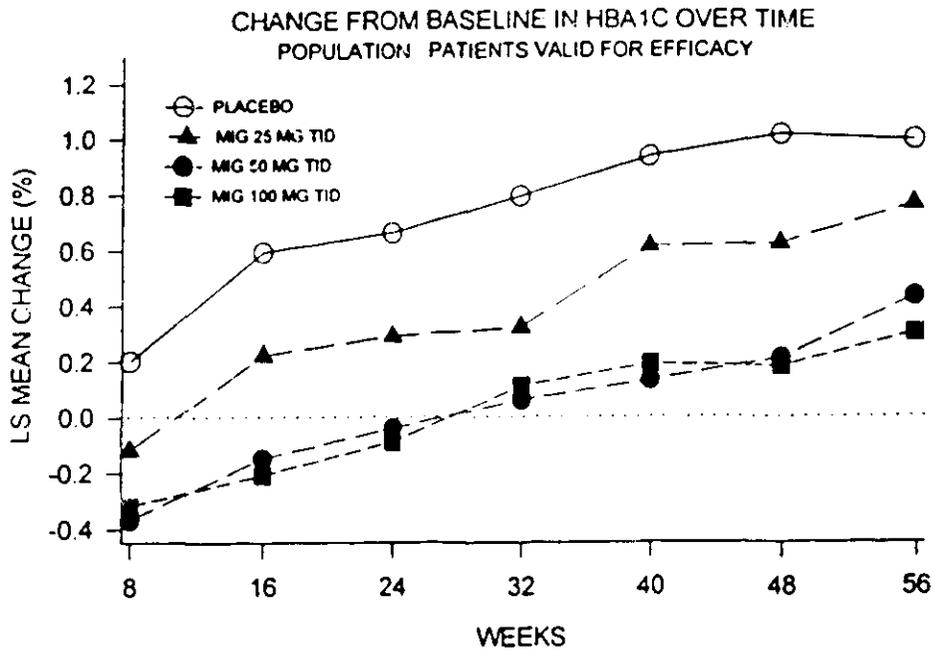
D92 - 006

Miglitol with Maximum Doses of Sulfonylurea

This was a multicenter double-blind study in patients inadequately controlled on maximum doses of sulfonylureas in NIDDM patients whose HbA1c was between 7 - 11% and who had been on a maximum dose of a sulfonylurea (20 mg of Glyburide, 40 mg of glipizide, 500 mg of chlorpropamide, 1000 mg of tolazamide, and 3000 mg of tolbutamide) for the 28 days before the study. They were pretreated with 10 mg bid of glyburide for six weeks before starting miglitol 25 mg tid, 50 mg tid 100 mg tid or placebo for 56 weeks. The drop out rate did not differ significantly among the treatment arms, but the reasons patients dropped out did differ significantly. Of the 118 patients randomized to placebo there were 30 patients (25%) who dropped out of the study, 12 because of inadequate therapeutic effect and 7 because of adverse events. Among the 39 patients randomized to miglitol 100 mg tid, 39 dropped out (34%), 3 due to inadequate therapeutic effect and 24 due to adverse events. There was one death due to a myocardial infarction followed by cerebrovascular accident.

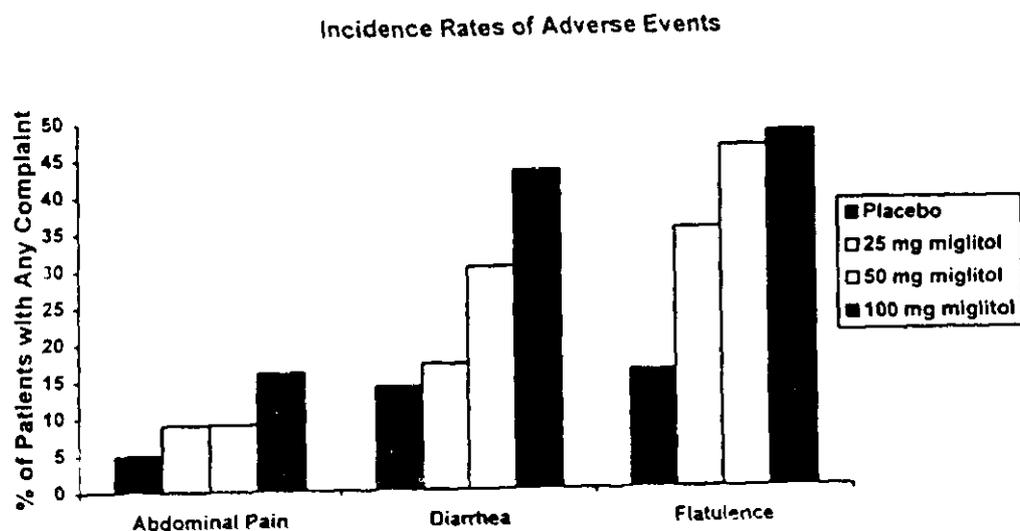
Using patients valid for efficacy, there was a mean rise in HbA1c in all groups, but the rise was significantly less in patients on miglitol 50 mg tid and 100 mg tid. Placebo subtracted change in HbA1c from baseline was -0.30, -0.62, and -0.73 % units for miglitol 25mg, 50 mg and 100 mg tid respectively. A time course of the effect is shown in the figure. Using the intent to treat population, the placebo subtracted difference at the last visit for the miglitol 25, 50, and 100 mg tid groups were -0.45, -0.78, and -0.83 % units respectively.

The mean HbA_{1c} levels by visit are plotted in the figure below:



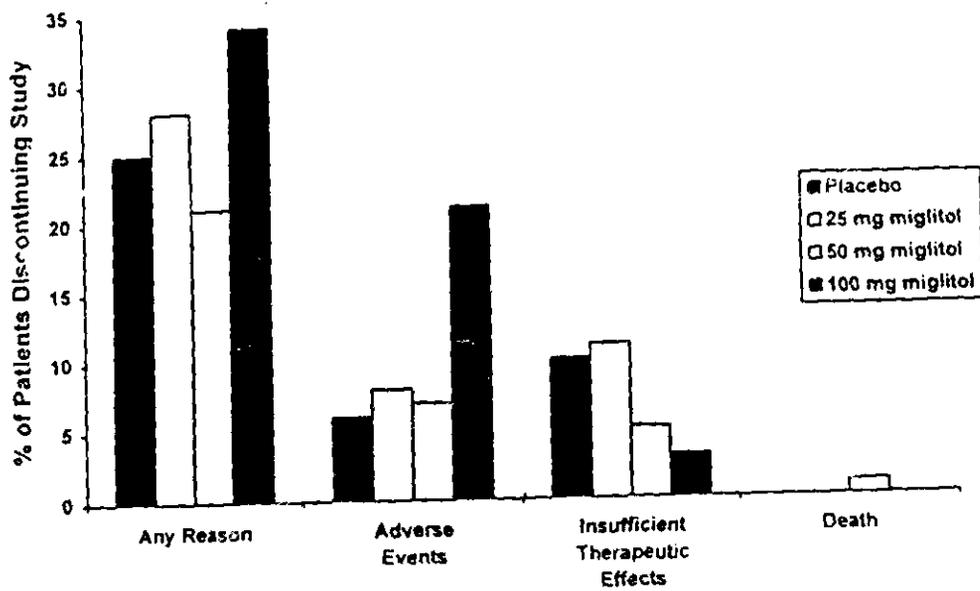
Among the secondary variables of efficacy there were dose- dependent falls in postprandial glucose and insulin. The fall in 24 hour urinary glucose was particularly impressive, going from 26.57 gm/gm creatinine in placebo patients to 5.08 gm/gm creatinine in patients on 100 mg miglitol tid($p=0.0001$). There was no significant relationship between miglitol blood levels and its effect on HbA1c.

As shown in the figure, miglitol treatment resulted in a dose-dependent increase in gastrointestinal complaints (abdominal pain diarrhea and flatulence) which were severe enough to cause a significant number of dropouts at the highest dose. There was also an unexplained decrease in respiratory complaints (rhinitis and sinusitis).



The small increase in efficacy going from 50 mg tid to 100 mg tid was associated with a large increase in gastrointestinal complaints. In the benefit/risk section it is stated "the conclusion of this analysis seems to point unequivocally to the 50 gm tid dose as the most favorable from the point of view of offering the greatest benefit for the least risk. for patients in this study". section 10.3 vol 227 page 108

Rates of Discontinuation



Study D87-0056

Monotherapy with Miglitol 50 mg and 100 mg tid in NIDDM

This was a study of NIDDM patients whose previous therapy was diet alone. They received miglitol 50 mg tid or 100 mg tid or placebo for 14 weeks after a 6 week run-in period. Patients were stratified to the three arms based on the initial HbA1c of less than 9.0% or greater than or equal to 9.0%. Patients with SGOT greater than 2x normal, creatinine value above 2 mg/dl, or hemoglobin less than 11.0 gm/dl were excluded. Initially, patients were to have been obese (120 - 180 % ideal body weight) but the protocol was amended to include patients with NIDDM regardless of weight, provided that they were not ketosis prone. Hemoglobin A1c had to be greater than 6.5% but not more than 12 %. The primary measure of efficacy was change in hemoglobin A1c from baseline. Secondary variables were changes in glucose and insulin levels after a standard 600 calorie breakfast consisting of juice, skim milk, eggs (or cheese), bread and cereal (50% CHO, 20% protein, 30% fat). Lipid levels were also measured.

Data for patients groups valid for efficacy are shown in the table. These groups consisted of 58 patients on placebo, 57 on miglitol 50 mg tid and 51 on miglitol 100 mg tid. The patients were about 56 years old and the numbers of men and women were approximately the same. Patients in both miglitol groups were 4% black compared to 7% black in the placebo group. Patients on miglitol had an average duration of diabetes of 5 years compared to 7 years for placebo patients. The mean HbA1c rose 0.47 % units in placebo patients but fell in patients on miglitol 50 mg tid and 100 mg tid, 0.22% units and 0.29%units respectively. The treatment effects (mean on active drug minus mean on placebo) of 0.69% units on miglitol 50 mg tid and 0.75 % units on miglitol 100 mg tid were significantly different from placebo ($p = 0.0001$) but were not significantly different from each other. Miglitol treatment was also associated with falls in postprandial glucose and insulin, although fasting levels were not significantly different. There also were no significant differences in total, LDL or HDL cholesterol, total triglycerides or body weight.

3 % of patients on miglitol 100mg tid discontinued prematurely compared to 6% of patients on 50 mg tid and 6% of patients on placebo. There were two serious events, both of which occurred in patients on placebo. The overall adverse event rates were 33% for patients on placebo, 64% for patients on Miglitol 50 mg tid and 76% of patients on miglitol 100 mg tid. Events relating to the gastrointestinal system were 16%, 52% and 71% for patients on placebo, miglitol 50 mg tid and miglitol 100 mg tid respectively. Elevation of SGPT greater than 1.8 x normal occurred in 3% of placebo patients, 3% of patients on miglitol 50 mg tid and 2% of patients on miglitol 100 mg tid.

D 87 - 056

<u>VARIABLES</u>	<u>PLACEBO</u>	<u>MIGLITOL 50MG TID</u>	<u>MIGLITOL 100MG TID</u>
HBA1C(%)	0.47 AB	-0.22	-0.28
Fasting plasma glucose (mg/dl)	18.93	8.34	2.98
60 min plasma glucose (mg/dl)	14.76	-51.58	-59.40
60 min plasma glucose rise (mg/dl)	-4.83 AB	-61.53	-65.50
90 min plasma glucose (mg/dl)	26.09 AB	-35.06	-48.48
90 min plasma glucose rise (mg/dl)	10.97 AB	-49.88	-52.13
120 min plasma glucose (mg/dl)	16.09 AB	-23.67	-30.30
120 min plasma glucose rise (mg/dl)	0.08 AB	-39.25	-31.96
Plasma glucose AUC (mg-min/dl)	2159.13 AB	-3146.2	-5565.2
Plasma glucose CMAX (mg/dl)	22.06 AB	-37.12	-47.98
Fasting serum insulin (uIU/ml)	-0.83	-0.43	-4.22
60 min serum insulin (uIU/ml)	0.45 AB	-9.33	-13.92
60 min serum insulin rise (uIU/ml)	2.45 AB	-8.18	-12.06
90 min serum insulin (uIU/ml)	-1.95 AB	-10.40	-16.33
90 min serum insulin rise (uIU/ml)	0.19 AB	-9.18	-14.96
120 min serum insulin (uIU/ml)	-4.57	-5.33	-14.49
120 min serum insulin rise (uIU/ml)	-2.83	-4.29	-12.03
Serum insulin AUC (uIU-min/ml)	-209.84 B	-887.10	-1567.6
Serum insulin CMAX (uIU/ml)	-1.97 B	-10.35	-17.22
Total triglycerides (mg/dl)	46.02	-9.88	0.68
Total cholesterol (mg/dl)	6.48	13.48	6.84
HDL cholesterol (mg/dl)	-1.03	-0.16	0.65
LDL cholesterol (mg/dl)	2.48	7.33	0.89
Fasting Weight (kg)	-0.76	-0.53	-0.77

A: significantly different from miglitol 50mg TID.
 B: significantly different from miglitol 100mg TID.

Study D87-057R

Miglitol in NIDDM Patients Inadequately Controlled on Maximal Sulfonylurea Therapy

This was a 26 week study in NIDDM patients age 30 or older who were inadequately controlled on maximal doses of SFU's. Inclusion required that patients' baseline HbA1c be greater than 6.5% but not more than 12%. Fasting blood glucose could not exceed 250 mg/dl. In addition to continuation of the SFU, patients were randomized into three groups: miglitol 50 mg tid, miglitol 100 mg tid and placebo. Patients were stratified based on entry HbA1c of less than 9.0% or greater. Change in HbA1c was the primary measure of efficacy, including measure of the proportion of patients who improved (fall in HbA1c of 1.0% unit) or worsened (rise in HbA1c by 1.0% unit). In addition, changes in glucose and insulin levels after a standard breakfast (521 calories, 67% CHO, 20% fat, 13% protein) were also monitored. Patients had an average age of 59 years and duration of diabetes of about 9 years. There were more male patients in the miglitol groups (67% on 50 mg tid and 55% on 100 mg tid) compared to placebo (48%), but no difference between the sexes existed with respect to efficacy measures at baseline. As submitted on February 7, 1996 the distribution of the various sulfonylureas among patients randomized to placebo were 48% glyburide, 25% glipizide, 21% chlorpropamide, 5% tolazamide, and 2% tolbutamide. The distribution among patients randomized to 50 mg or 100 mg tid of miglitol were similar.

As shown in the table, mean HbA1c went up in the placebo group but fell in both miglitol groups. The treatment effect for miglitol 50 mg tid was -0.82% units, and for 100 mg tid was -0.74% units. Postprandial glucose and insulin levels also fell in the miglitol groups vs placebo as did fasting serum triglyceride. No differences in mean data were seen between the two doses of miglitol. 5% of the placebo patients had a fall in HbA1c of 1.0 or more, compared to 36% of patients on miglitol 50 mg tid and 28% on 100 mg tid. The difference between placebo and both doses of miglitol were statistically significant but no difference existed between the two doses of miglitol. Likewise, a significant difference between miglitol and placebo existed in the

proportion of patients whose HbA1c rose by 1.0% unit or more (16% of placebo patients, 5% on miglitol 50 mg tid and 4% on miglitol 100 mg tid).

D.87-057

	<u>PLACEBO</u>	<u>MIGLITOL 50MG TID</u>	<u>MIGLITOL 100MG TID</u>
HbA1c (%)	0.33 AB	-0.49	-0.41
Fasting plasma glucose (mg/dl)	6.82	-9.88	-1.91
60 min plasma glucose (mg/dl)	-1.25 AB	-69.41	-72.75
60 min plasma glucose rise (mg/dl)	-3.14 AB	-58.82	-71.29
90 min plasma glucose (mg/dl)	-0.50 AB	-58.22	-69.33
90 min plasma glucose rise (mg/dl)	-6.59 AB	-48.33 B	-67.45
120 min plasma glucose (mg/dl)	-6.51 AB	-53.27	-48.02
120 min plasma glucose rise (mg/dl)	-13.26 AB	-42.60	-45.64
Plasma glucose AUC (mg-min/dl)	-457.52 AB	-6141.5	-6262.2
Plasma glucose CMAX (mg/dl)	-3.83 AB	-60.76	-67.60
Fasting serum insulin (uIU/ml)	1.86	-0.30	-0.23
60 min serum insulin (uIU/ml)	0.77 AB	-6.46	-9.34
60 min serum insulin rise (uIU/ml)	-1.02 AB	-6.29	-9.02
90 min serum insulin (uIU/ml)	-1.55 A	-10.17	-7.93
90 min serum insulin rise (uIU/ml)	-3.46 A	-9.86	-7.73
120 min serum insulin (uIU/ml)	-2.76	-5.16	-5.47
120 min serum insulin rise (uIU/ml)	-4.41	-5.11	-5.24
Serum insulin AUC (uIU-min/ml)	-74.50 B	-630.15	-779.20
Serum insulin CMAX (uIU/ml)	-0.33 AB	-9.13	-8.01
Triglycerides (mg/dl)	12.05 A	-30.49	-19.91
Total cholesterol (mg/dl)	6.23	1.55	9.18
HDL cholesterol (mg/dl)	0.34	1.24	0.35
LDL cholesterol (mg/dl)	4.35	1.43	11.93

A: Significantly different from miglitol 50 mg t.i.d..

B: Significantly different from miglitol 100 mg t.i.d..

Adverse events were reported in 37% of placebo patients, 66% of the miglitol 50 mg tid patients and 75 % of the miglitol 100 mg tid patients. Most of the adverse events on miglitol were related to the gastrointestinal system. As shown in the table, the incidence of gastrointestinal complaints was dose dependent and was severe enough to cause 5% of patients on 50 mg tid and 15% of patients on 100 mg tid to drop out.

	Placebo (%)	Miglitol 50 mg tid (%)	Miglitol 100 mg tid (%)
Abdominal pain	2/62 (3)	5/61 (8)	13/68 (19)
Diarrhea	6/63 (10)	12/61 (20)	33/68 (49)
Flatulence	12/62 (19)	29/60 (48)	41/68 (60)
drop out due to GI adverse event	0	3/61 (5)	10/68 (15)

COMPARATIVE STUDIES

Study 0288

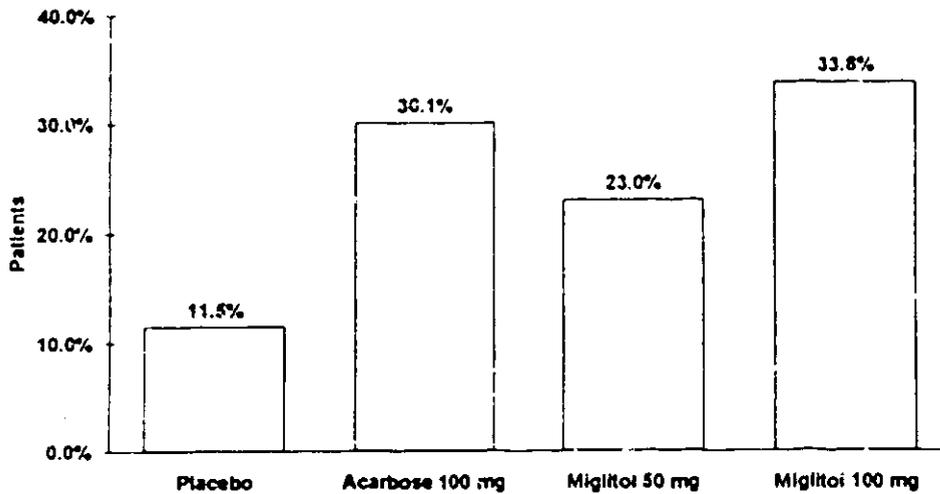
Miglitol vs Acarbose

This study was performed in Germany, Switzerland and the Czech Republic to compare miglitol at 50 and 100 mg tid to acarbose 100 mg tid and placebo. Patients were ages 40 - 75 had NIDDM with HbA1c 6.5 - 9.0%, and who had not received drug therapy in the previous three months. After a 2 week run-in period patients were assigned to one of four groups: miglitol 50 mg tid, miglitol 100 mg tid, acarbose 100 mg tid or placebo. The duration of drug treatment was 24 weeks. During the first two weeks, patients assigned to acarbose received 50 mg tid and the dose was then increased to 100 mg tid starting with week three. Similarly, patients assigned to miglitol 100 mg tid, received 50 mg tid for the first two weeks and the dose was doubled starting with week three. Patients assigned to miglitol 50 mg tid received that dose for the entire 24 week period. Compared to placebo, the treatment effect on HbA1c was -0.43 % units ($p=0.002$), -0.42 % units($p=0.0022$), -0.54 %units ($p=0.0001$) for acarbose 100 mg tid, miglitol 50 mg tid and 100 mg tid respectively. The difference between the two doses of miglitol were not statistically significant. Similarly, the treatment effect on postprandial glucose was also significant for all three active treatment arms but no differences existed among the three active treatments.

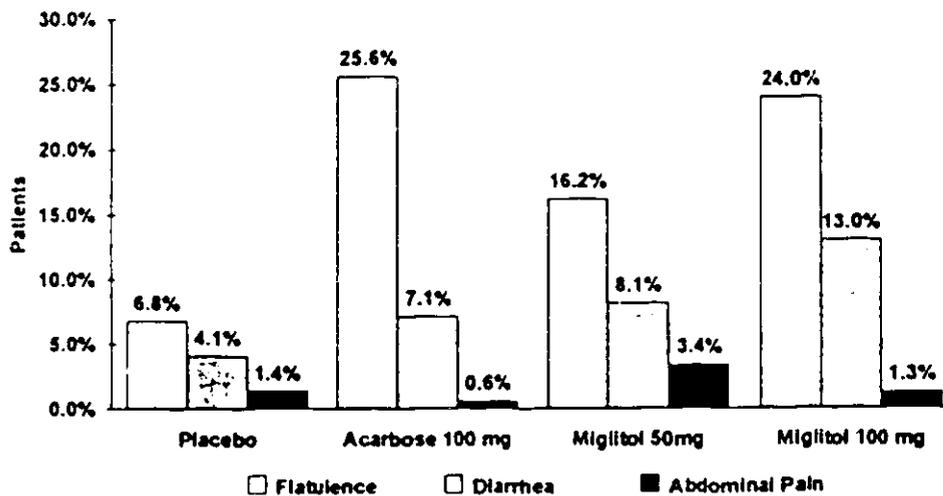
Adverse events were reported in 23% of placebo patients, 38.5% of patients on acarbose, and 29.7% and 39.6% of patients on miglitol 50 mg tid and 100 mg tid respectively. As shown in the figure, most of the AE's were related to the gastrointestinal system. All groups on active treatment had significantly more gastrointestinal complaints than the placebo group. There was no difference among the three active treatment arms, although reports of adverse events appeared somewhat less in patients on miglitol 50 mg tid than on 100 mg tid. Premature discontinuation due to an adverse event occurred in 5.4 % of patients on placebo, 8.3% on acarbose 100 mg tid, 6.1% on miglitol 50 mg tid and 8.4% of patients on miglitol 100 mg tid. Patients who left the

trial because of an adverse event related to the gastrointestinal system were 3 patients on placebo, 11 on acarbose 100 mg tid, 6 on miglitol 50 mg tid and 10 on miglitol 100 mg tid.

02 PP

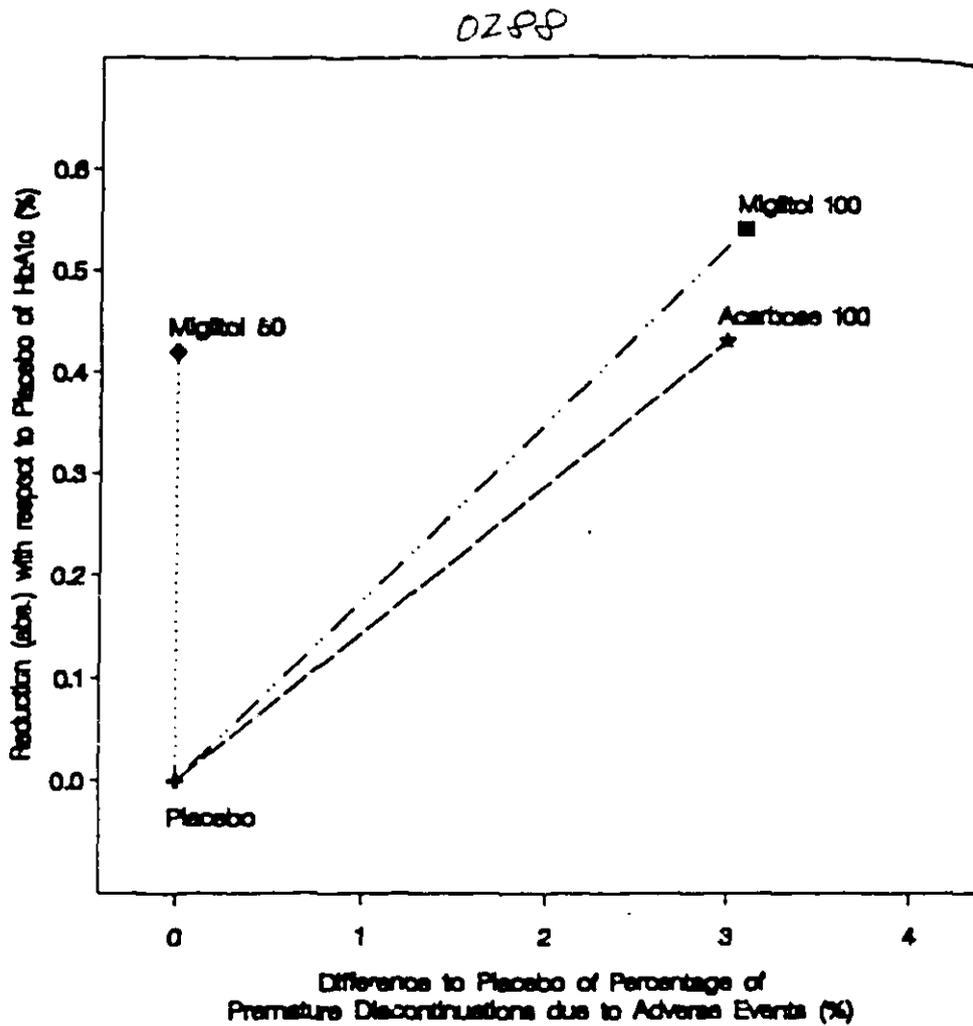


Overview of gastrointestinal adverse events typical for glucosidase inhibitors (n = 606)



Overview of the three main adverse events typical for glucosidase inhibitors (n = 606)

The results of this study shows that acarbose 100 mg tid and miglitol 100 mg tid are roughly equivalent with respect to efficacy and adverse events. At a miglitol dose of 50 mg tid there is nearly the same efficacy but less adverse events. We do not have a comparison of miglitol and acarbose each at 50 mg tid. The Sponsor displays the favorable benefit vs risk relationship for miglitol 50 mg tid in the figures and concludes that " miglitol 50 mg seems to be superior to the other two treatments in terms of its benefit risk ratio."



Study 307

Miglitol vs Glibenclamide

This study, conducted in Germany and Austria, compared the efficacy and tolerability of miglitol and glibenclamide vs placebo in type 2 diabetics, age 30-70, who had diabetes for at least 3 months and whose HbA1c was between 7.5 and 9.5% on diet therapy alone. During a 4 week run-in period patients received the miglitol placebo tid and the glibenclamide placebo qd. The patients were then randomized into one of three groups: active miglitol + glibenclamide placebo (this group is referred to later as "miglitol"), miglitol placebo + active glibenclamide (referred to as "glibenclamide") and miglitol placebo + glibenclamide placebo (referred to as 'placebo'). The starting doses of miglitol and glibenclamide were 50 mg tid and 3.5 mg qd respectively. The dose of miglitol was increased to 100 mg tid after four weeks of double-blind study and continued for the remaining 20 weeks. The dose of glibenclamide could have been doubled after four weeks, but was not. The final comparison is therefore 20 weeks of miglitol 100 mg tid vs glibenclamide 3.5 mg qd vs placebo. Patients who completed the study are referred to as "per protocol" and consisted of 42 on placebo, 40 on miglitol and 37 on glibenclamide. The 'intent to treat' analysis included patients who did not have the second HbA1c at the end of the study. In this group there were 64 on placebo, 61 on miglitol and 61 on glybenclamide. As shown in the table, both miglitol and glibenclamide were significantly different from placebo. Glibenclamide appeared more effective than miglitol but the difference was only significant ($p = 0.0332$) in the "intent to treat" patients:

Study 307

	per protocol		intent to treat	
	treatment effect, HbA1c % units	p value	treatment effect, HbA1c % units	p value
placebo-miglitol	0.75	0.0021	0.79	0.0004
placebo- Glibenclamide	1.01	0.0001	1.27	0.0001
Miglitol- Glibenclamide	0.26	0.2964	0.48	0.0332

Postprandial glucose levels were decreased with both miglitol and glibenclamide relative to placebo, but insulin levels were increased with glibenclamide and decreased with miglitol. Mean weight change was + 1.4 kg with glibenclamide, -1.4 kg with miglitol, and + 0.04 kg with placebo. These differences were not statistically different due to the large variability among patients. No difference in triglyceride level was observed.

Of the 29 patients who left the study prematurely, 6 were on placebo, 12 on miglitol and 11 on glibenclamide. Six patients left the study because of adverse events, 1 on placebo (metastatic cancer) 3 on miglitol (gastrointestinal symptoms) and 2 on glibenclamide (sleep disturbance in one, and unstable angina in the other). 45 patients had at least one adverse event, 14 on placebo, 18 on miglitol, and 13 on glibenclamide

In summary, this study shows that miglitol 100 mg tid was nearly as potent as glibenclamide 3.5 mg qd with respect to efficacy and tolerability over the 24 weeks of treatment. However, glibenclamide was associated with a rise in insulin level while miglitol was associated with a fall of insulin levels. There was also a trend for weight gain with glibenclamide and weight loss with miglitol. Miglitol 100 mg tid and glibenclamide 3.5 mg qd had similar tolerability.

Study 0277

Miglitol vs Glibenclamide

This was a 24 week study of miglitol vs glibenclamide in NIDDM patients conducted in Italy. Following a six week run-in, patients were randomized to receive miglitol or glybenclamide. For the first 4 weeks the miglitol group received 50 mg tid of miglitol plus the glybenclamide placebo qd. The glybenclamide group received 2.5 mg qd of active drug plus the miglitol placebo tid. For the next 20 weeks, the miglitol group received 100 mg tid plus glybenclamide placebo. The glybenclamide group received 5 mg qd of glybenclamide and miglitol placebo tid. There was no double placebo group which received no active drug. As shown in the table, both groups experienced a significant fall in HbA1c. The change was greater for glybenclamide but the difference was not statistically significant. Patients on miglitol experienced a greater fall in postprandial glucose, but again the difference was not significant. The only significant difference between the groups was with respect to postprandial insulin levels which rose in patients on glybenclamide but fell in patients on miglitol.

	LSMEAN	MIGLITOL MEAN	LSMEAN	GLYBENCLAMIDE MEAN
HbA1c (%)	-0.78*	-0.72	-1.18*	-1.13
GLYCEMIA AUC	-5011*	-4842	-3350*	-3400
INCREMENTAL GLYCEMIA AUC	-2346*	-2456	-338	-801
INSULIN AUC	-1257**	-1177	1178	1144
INCREMENTAL INSULIN AUC	-846	-782	388	208

* RELEVANT DIFFERENCE FROM 0 (EXPLORATIVE P<0.05)

** RELEVANT DIFFERENCE FROM GLYBEN. (EXPLORATIVE P<0.05)

19% of patients on miglitol and 21% of patients on glybenclamide reported adverse events. One miglitol patient dropped out of the study because of AE. As expected, adverse events with miglitol were flatulence and diarrhea. With glybenclamide AE's were asthenia, languor and hunger.

Study 0264

Miglitol versus metformin in obese patients with NIDDM

This study was conducted in Paris in NIDDM patients age 30-70 who had a body mass index greater than 120% normal. After a one week run in period, patients were started on 100 mg bid of miglitol or 850 mg qd of metformin. After 15 days the dose of miglitol was increased to 100 mg tid and metformin to 850 mg bid. There were no placebos. The duration of treatment was 6 months. The intent to treat groups consisted on 85 patients in the miglitol group and 81 in the metformin group. The protocol compliant group consisted of 76 patients on miglitol and 76 on metformin. Premature terminations occurred in 26.7% of miglitol patients and 18.2% of metformin patients. Among miglitol patients, 16 terminated prematurely because of AE's, 10 because of lack of efficacy and 8 for other reasons. Among metformin patients 10 terminated because of AE's, 7 because of lack of efficacy and 4 for other reasons. Adverse events leading to premature terminations primarily involved the gastrointestinal tract in both groups.

As shown in the table below, metformin was better than miglitol with respect to reduction in HbA1c and glucose levels. Miglitol was more effective in reducing postprandial insulin levels. No difference was observed in serum triglycerides. Patients in both groups lost about 2 kg.

0264

Table A: Analysis of efficacy in intent-to-treat population

Parameter	Treatment	Initial value	End of treatment value [∇]	p
HbA1c ⁺ (%)	migliol	6.96 ± 1.72	6.79 ± 1.46	0.01
	metformin	6.89 ± 1.82	6.22 ± 1.44	
Fasting blood glucose ⁺ (mmol/l)	migliol	11.27 ± 3.48	11.19 ± 3.12	0.003
	metformin	11.07 ± 3.90	9.77 ± 3.05	
Blood glucose 60' pp ⁺ (mmol/l)	migliol	15.51 ± 4.55	13.55 ± 4.70	0.97
	metformin	15.26 ± 4.38	13.57 ± 3.94	
Blood glucose 120' pp ⁺ (mmol/l)	migliol	14.19 ± 4.99	13.17 ± 4.14	0.04
	metformin	14.20 ± 4.99	11.89 ± 3.99	
AUC blood glucose (0'-120') ⁺ (mmol/l.h)	migliol	1702 ± 508	1544 ± 453	0.25
	metformin	1674 ± 515	1466 ± 425	
Weight ⁺ (kg)	migliol	86.7 ± 15.5	85.5 ± 4.6	0.36
	metformin	88.3 ± 16.2	84.5 ± 4.5	

⁺ mean ± standard deviation [∇] mean: adjusted by ANCOVA

Parameter	Treatment	Initial value	End of treatment value	p [∇]
Fasting plasma insulin [*] (IU/l)	migliol	19 (11-28)	16.5 (11-27)	0.36
	metformin	19 (11-32)	19 (11-33)	
Plasma insulin 60' pp [*] (IU/l)	migliol	58 (31-99)	37 (21-81)	0.006
	metformin	60.5 (26-102)	55 (34.5-55)	
Plasma insulin 120' pp [*] (IU/l)	migliol	40 (25-72)	37.5 (19-74)	0.86
	metformin	51 (31-104)	42 (24-76)	
AUC plasma insulin [*] (0'-120') (IU/l.h)	migliol	5490 (3000-9270)	4110 (2520-8160)	0.01
	metformin	5370 (2865-11385)	5235 (3450-8580)	

^{*} median (1st quartile - 3rd quartile) [∇] results from analysis of covariance

As shown in the table, there was a high incidence of gastrointestinal AE's in both groups. The only significant difference was with respect to flatulence which occurred in 37.8% of patients on miglitol compared to 10.2% of patients on metformin

TYPE OF EVENT COSTART terminology	MIGLITOL n = 90		METFORMIN n = 88		p
	n	%	n	%	
Flatulence	34	37.8	9	10.2	p > 0.001
Diarrhea	28	31.1	25	28.4	n.s.*
Abdominal pain	9	10.0	8	9.1	n.s.*
Nausea	6	6.7	5	5.7	n.s.*
Constipation	2	2.2	4	4.6	n.s.*
Colitis	3	3.3	2	2.3	n.s.*
Vomiting	2	2.2	0	0	n.s.*
Dyspepsia	1	1.1	0	0	n.s.*
Eructation	0	0	1	1.1	n.s.*
Glossitis	0	0	1	1.1	n.s.*
Tongue disorder	0	0	1	1.1	n.s.*
Anorexia	0	0	1	1.1	n.s.*

* n.s. = p > 0.05

Study 306

Migliitol versus Metformin in patients inadequately managed on a Sulfonylurea

This was a European study of patients with NIDDM who were on glybenclamide 7 - 20 mg per day and still were inadequately controlled as manifested by HbA1c of 7.5 - 11.0. Patients were aged 30-70. The glybenclamide was continued through the study and was not to be changed unless reduction was required because of hypoglycemia. There was a four week placebo run-in after which patients were treated with miglitol 50 mg tid plus metformin placebo, metformin 850 mg qd plus miglitol placebo, or both placebos with no active test drug. After 4 weeks, the doses of active drug were increased to 100 mg tid for miglitol and 850 mg bid for metformin. These doses were continued for 20 weeks. For intent to treat analysis there were 54 patients in each group. Completing the protocol were 43 patients on placebo, 48 on miglitol and 49 on metformin. In the placebo group there was one drop out because of gastrointestinal symptoms and two dropouts due to lack of efficacy. In the miglitol group these were three dropouts due to gastrointestinal symptoms and none due to lack of efficacy. In the metformin group there were two dropouts due to GI symptoms and 1 due to lack of efficacy. All other dropouts were not due to effects of the drugs.

As shown in the figure, both drugs caused a reduction in HbA1c relative to placebo, but metformin was more effective than miglitol. Both drugs were more effective in patients on 10 mg or less of glybenclamide than in patients on greater than 10 mg of glybenclamide, but metformin was more effective than miglitol in both groups (see table). Fasting plasma glucose was lowered more by metformin than by miglitol, but the two drugs had equivalent effects on postprandial glucose. Insulin values tended to be lower in patients on either active drug but the differences were not statistically significant. No significant differences were observed for triglycerides.

BAY M 1099 / STUDY NO. 306
 LS-MEANS OF HbA_{1c} AT ENDPOINT ADJUSTED TO BASELINE (±)
 PATIENTS VALID FOR PER PROTOCOL EFFICACY ANALYSIS

B
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LS-MEANS OF HbA_{1c} AT ENDPOINT
 ADJUSTED TO BASELINE

DIFFERENCES OF ADJ. LS-MEANS
 OF HbA_{1c} TO PLACEBO

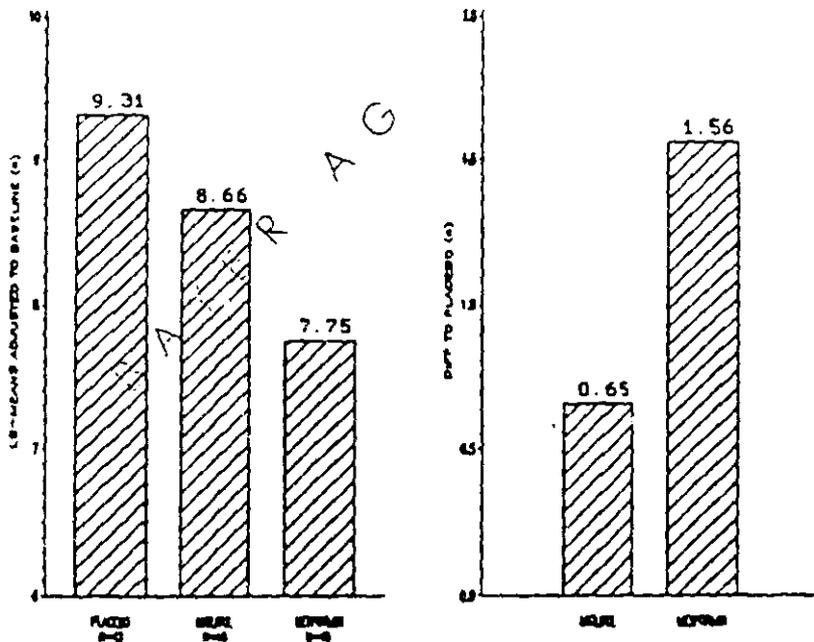


TABLE P: PLACEBO SUBTRACTED DIFFERENCE OF LS-MEANS FOR HbA_{1c}

306

	per protocol		intent-to-treat	
	>5 mg to ≤10 mg	>10 mg	>5 mg to ≤10 mg	>10 mg
miglitol	0.67	0.47	0.46	0.78
metformin	1.89	1.20	1.84	1.40

A table of adverse events is shown below. This study differs from other studies in the NDA in that the total reporting of adverse events is very low. However, gastrointestinal complaints with miglitol were still evident.

Study 306

	placebo	miglitol	metformin
diarrhea	0	6	3
flatulence	0	11	5
abdominal pain	1	2	1
n	54	54	54

Safety Update filed April 26, 1996

The following studies have been completed since the original NDA data base closed:

0298 (Italy) - One year parallel study of miglitol 100 mg tid (n=46) vs placebo (n=46) in IDDM patients

0308 (Canada) - One year parallel study of miglitol 50 mg (n=95), 100 mg (n=91) and placebo (n=93) in patients with IDDM

X 0306 (multinational European) - 18 month extension of the original six month comparison of miglitol 100 mg tid vs metformin 850 mg bid in SFU treated patients with NIDDM. There were 38 patients on placebo enrolled in the extension study and 44 patients on miglitol.

Total Patient Exposure to Miglitol

U.S.	NDA and Present	
less than six months	488	
six months or longer	474	

total	962	

Non- U.S.	NDA	Present
less than six months	1450	1502
six months or longer	952	1151
	-----	-----
total	2402	2653

Of the 251 new patients in non-US studies, 15% were NIDDM and 85% were IDDM. As shown in the table the distribution of adverse events does not differ between the 2402 patients in the original NDA or the 2653 patients in the update except for a small increase in reports of arthralgia which occurred in both miglitol and placebo patients. No difference was observed between miglitol and placebo with respect to elevation of liver enzymes.

<u>Adverse Event</u>	<u>NDA</u>		<u>Update</u>	
	Placebo (N=1745)	Miglitol (N=2402)	Placebo (N=1902)	Miglitol (N=2653)
Body as a whole				
Abdominal Pain	108 (6.2%)	279 (11.6%)	159 (8.4%)	400 (15.1%)
Digestive				
Diarrhea	98 (5.6%)	519 (21.6%)	135 (7.1%)	635 (23.9%)
Dyspepsia	43 (2.5%)	67 (2.8%)	64 (3.4%)	118 (4.4%)
Flatulence	285 (16.3%)	932 (38.8%)	332 (17.5%)	1077 (40.6%)
Hemorrhage				
Eye Hemorrhage	0	1 (0.1%)	3 (0.2%)	6 (0.2%)
Menorrhagia	0	1 (0.1%)	0	4 (0.2%)
Hematuria	0	1 (0.1%)	0	3 (0.1%)
Metabolic/Nutritional				
Hypoglycemia	25 (1.4%)	49 (2.0%)	71 (3.7%)	122 (4.6%)
Musculoskeletal				
Arthralgia	8 (0.5%)	15 (0.6%)	33 (1.7%)	71 (2.7%)

There were four additional deaths, three in patients on miglitol and one in a patient on placebo. The distribution of deaths in all patients in non-US studies is shown in the table. No difference was seen between miglitol and placebo.

Causes of Death of Patients in Updated Non-US Safety Pool 2

	PLACEBO (n=1902)	MIGLITOL (n=3918)*
Myocardial Infarction	1 (0.05%)	4 (0.1%)
Cerebrovascular Accident	1 (0.05%)	4 (0.1%)
Heart Failure	1 (0.05%)	2 (0.05%)
Other Causes	5 (0.3%)	9 (0.2%)
Total	8 (0.4%)	19 (0.5%)

* Includes all miglitol-treated patients, including those from uncontrolled studies

There were four deaths in miglitol patients and two deaths on placebo for which a cause was not given.

PACKAGE INSERT

Background, preclinical studies, and pharmacokinetics issues are adequately discussed.

The clinical experience sections shows the results of pivotal studies with respect to hemoglobin A1c and 1 hour post-prandial glucose using miglitol as monotherapy and in combination with sulfonylureas. Pooled data are shown for the dose-response relationships from 25 mg to 200 mg tid although the maximal recommended dose is 100 mg tid. The description of adverse events is adequate. It deals mostly with the gastrointestinal complaints but also mentions the increased rash and low serum iron levels. Why miglitol should not be used in patients with renal insufficiency is clearly stated.

The section on dosage and administration recommends an initial starting dose of 25 mg tid. It recommends that the dose be increased to 50 mg tid after about four weeks and that HbA1c be measured after about three months to gauge therapeutic response. Increasing the dose to 100 mg tid is then recommended if a satisfactory therapeutic response had not been obtained with 50 mg tid. This section ends with the statement that the maximal dose is 100 mg tid. A dose of 200 mg tid may give better glycemic control but with increased gastrointestinal symptoms and is therefore not recommended.

The only criticism of the proposed label is that it gives the impression that the dose-response relationship was clearly established, and that increasing the dose from 50 mg to 100 mg tid would generally be expected to improve efficacy. In fact, this is not really the case. In the only study using four different doses of miglitol (25, 50, 100 and 200 mg tid in study 0231) the effectiveness of the 50 mg tid dose was unexpectedly low so that 100 mg tid appeared much more effective by comparison. However, there are four studies comparing 50 mg tid and 100 mg tid which show no difference in efficacy, but do show a difference in tolerability. Indeed, the PI's study 92-006 and of study 0288 state in their reports that consideration of efficacy and tolerability favors the 50 mg tid dose over the 100 mg tid dose.

REVIEWER'S CRITIQUE AND RECOMMENDATION:

The data presented in the NDA clearly establish that miglitol is safe and effective for treatment of hyperglycemia in NIDDM patients either as monotherapy or in combination with sulfonylureas. With respect to use with sulfonylureas, miglitol improved glycemic control in patients on maximal doses of sulfonylureas as well as in patients on average doses. In addition, miglitol blocked the hyperinsulinemia that is seen when sulfonylureas are used alone. As measured by HbA1c, miglitol has a drug effect of about 0.8 % units. This is roughly equivalent to the effect of acarbose, but less than what is usually observed with metformin or sulfonylureas. On the other hand the adverse event profile of miglitol is very favorable. No dangerous or serious adverse events have been reported in patients on miglitol. There is a high incidence of gastrointestinal complaints, particularly flatulence but these problems should really be considered inconveniences rather than hazards.

The efficacy and adverse event profile of miglitol is similar to that of acarbose. However, the dose-dependent elevation of liver enzymes observed with acarbose was not found with miglitol. Even at 200 mg tid, there was not even a suggestion that miglitol was causing increased SGOT or SGPT. This result is the opposite of what one would have expected because the absorption of miglitol is much greater than that of acarbose (50% vs less than 2% absorption of a 100 mg tablet). Despite the fact that there is substantial systemic exposure to miglitol, there was no evidence for any systemic toxicity. Nearly all of the adverse events reported with miglitol were related to its activity within the gut and are troublesome but not dangerous. Since the risk associated with miglitol therapy appears to be negligible, the benefit to risk ratio is clearly very high.

With respect to efficacy, miglitol is not as potent as metformin or sulfonylureas. One possible exception may be the use of miglitol in the elderly. There are two studies in which miglitol was more effective in older patients than in younger patients. For example, in 92-009, the drug effect (miglitol minus placebo) on hemoglobin A1c was -1.07% units in patients over 60

compared to -0.28 in patients aged 60 and younger. If this finding holds up, it would appear that miglitol's efficacy in elderly patients would be nearly the same as that of the sulfonylureas but with much more safety. A study comparing miglitol to glyburide in elderly patients is presently underway, but the results will not be ready in time to affect the initial labeling.

Miglitol is effective when used in combination with a sulfonylurea but is not as effective as metformin. There is insufficient data to comment on the use of miglitol in combination with insulin.

In summary the NDA provides adequate evidence that miglitol is safe and effective for treatment of hyperglycemia in patients with NIDDM. Among the 3072 patients who received miglitol in placebo-controlled studies (906 in the USA and 2166 outside the USA) reported in this NDA, there are no deaths or serious morbidity attributable to miglitol. The high incidence of flatulence and diarrhea may limit the drug's acceptability to American patients, but those who tolerate miglitol can expect an improvement in postprandial hyperglycemia associated with a reduction of about 0.8% units in hemoglobin A1c and an improvement in hyperinsulinemia as well.

The only remaining issue to be resolved at this time is the bioequivalency of the to-be-marketed formulation and the formulation that was used in the clinical trials. The statement in the package insert regarding dose-response characteristics should also be changed to emphasize that 50 mg tid is the standard dose and that pushing the dose to 100 mg tid will increase gastrointestinal complaints without much added efficacy in most patients. Otherwise, I see no major deficiencies in the application and recommend that the NDA be approved.



Robert I Misbin MD

Medical Officer

June 26, 1996

HF0510 - NDA 20-682

CC HF0510 / Misbin / Fleming / Fowler

Full review
62

Dr. J. ... 7/2/96

Statistical Review and Evaluation

AUG 21 1996

NDA #: 20-682
Applicant: Bayer
Name of Drug: Glyset (miglitol tablets)
Indication: Treatment of Type II diabetes mellitus (NIDDM)

Documents Reviewed: Volumes 1.1, 1.2, 1.137, 1.172, 1.208, 1.216, 1.127, 1.268, 1.285, and 1.351-1.352 dated January 22, 1996. A replacement data diskette was received August 2, 1996. A new Data diskette was received August 12, 1996.

This review pertains to five placebo controlled studies using miglitol as monotherapy in patients with NIDDM and three studies in patients on but not controlled by sulfonylureas.

The medical officer is R. Misbin MD (HFD-510), who has already completed his review and finds miglitol safe and effective.

Background

This review will mainly focus on analyses of HbA1c as presented in the integrated summary of efficacy. These analyses analyzed changes from baseline in HbA1c whereas the individual study reports had varying response variables. Some studies analyzed the HbA1c values themselves using an analysis of covariance. One study used log transformed values of HbA1c. Other studies used changes from baseline in HbA1c. These differing methods did not lead to differing conclusions. Therefore, focusing on the more consistent analyses seems appropriate.

Study Descriptions and Method of Analyses

The analyses discussed in this review will mainly focus on the per protocol (called valid for efficacy population by the sponsor) analyses of HbA1c with a valid value of HbA1c at defined endpoint. [It is not always an endpoint analysis of patients valid for efficacy. The sponsor used the term valid for efficacy for pooling for some of the studies. Studies D92-006 and D92-009 only included patients who had a one-year endpoint with a valid visit between weeks 40 through 56. Studies D87-056 and D87-057 only included patients who had a valid visit at weeks 8 or 14. Study 288 only included patients who had at least 20 weeks of treatment. The other studies were true endpoint analyses.] These

analyses correspond to the analyses presented in the sponsor's label (Table 1 and 2)). These analyses were analyses on changes from baseline in HbA1c with the identical factors included in the sponsor's original analysis model given in their study reports. Studies D87-056, D87-057 and D92-006 included investigator, stratum and treatment group as factors. Study D92-009 only included investigator and treatment group. Study 281 included investigator, treatment group, investigator by treatment group interaction and baseline HbA1c as a covariate. Studies 307 and 288 included treatment group and baseline covariate. Study 306 included country, treatment group and country by treatment group interaction with baseline HbA1c as covariate. In Study 306, the centers in Germany and Austria were pooled.

Results

Table 1 provides the results of the five monotherapy miglitol studies. Mean changes from baseline were significantly different from placebo in Study 0317 for miglitol 50 mg tid and in Study 0307 for miglitol 100mg tid. Both 50mg and 100mg tid were significantly different from placebo in Studies 0288 and 0295. In Study 0281 miglitol 100mg and 200mg tid were significantly different from placebo but the 25mg and 50mg tid doses were not. Significant differences from placebo were seen for all miglitol treatments in mean changes in 1-hour postprandial glucose.

The sponsor found a significant difference at baseline in HbA1c in Study 0281 with the placebo group having the lower mean. The sponsor's protocol defined analysis for this study was a analysis of covariance that gave similar results to the analysis in Table 1. The effect of the baseline difference was not very important in the light of a mean increase from baseline in the placebo group and mean decreases from baseline in the miglitol groups.

Table 2 presents the comparisons on miglitol versus placebo for changes in HbA1c in the three studies in patients using sulfonylurea. All doses of miglitol were significantly different from placebo in changes in HbA1c. Similar significance was also seen in mean changes in 1-hour postprandial glucose.

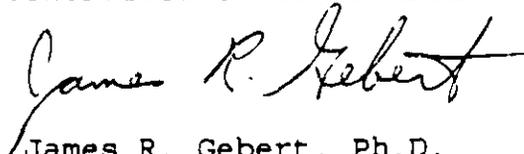
The sponsor's analyses addressed the multiple comparison issue. The non-significance of the 25mg and 50mg doses in Study 0281 was because they were not significant using either Dunnett's multiple comparison procedure (or alternatively a Bonferroni-Huff stepdown procedure). Significance of these doses were found in the sponsor's intent-to-treat analysis using both multiple comparison procedures.

Reviewer's Comments

This reviewer duplicated the sponsor's per protocol (valid for efficacy) analyses of valid HbA1c at defined endpoint. (Tables 1 and 2). The intent-to-treat analyses not discussed here showed efficacy also.

Although the sponsor was not consistent in factors included in their analyses or in the defined endpoint, most studies would show efficacy irrespective of the model used. Only Study-306 would not show efficacy for the miglitol versus placebo comparison if a different model was used. If investigator was used as a factor rather than country the results are not significant. However, the sample size here is small which might explain the lack of sensitivity to model choice.

The studies show miglitol to be effective as monotherapy and in patients already taking but not controlled on sulfonylureas.



James R. Gebert, Ph.D.
Mathematical Statistician HFD-715


Concur: Mr. Marticello

Dr. Nevius *JGN* 8/20/86

This review contains 3 pages of text and 2 pages of tables.

cc:
Orig NDA 20-682
HFD-510
HFD-510/Dr. Misbin
HFD-510/Mr. Johnston
HFD-344/Dr. Lisook
HFD-715/Dr. Nevius [Division 2 File]
HFD-715/Dr. Gebert
HFD-715/Mr. Marticello
Chron

Table 1
GLYSET Monotherapy Study Results

WEEKS	Study	Treatment	HbA1c (%)		1-hour Postprandial Glucose (mg/dL)	
			Mean Change from Baseline*	Treatment Effect**	Mean Change from Baseline	Treatment Effect**
56	1 (US) 092-009 (0317)	Placebo (N=76)	+0.71	---	+24	---
		GLYSET 50 mg t.i.d. (N=83)	+0.13	-0.58†	-39	-63†
14	2 (US) 087-056 (0295)	Placebo (N=56)	+0.47	---	+15	---
		GLYSET 50 mg t.i.d. (N=55)	-0.22	-0.69†	-52	-67†
		GLYSET 100 mg t.i.d. (N=49)	-0.28	-0.75†	-59	-74†
24	3 (non-US) (0281)	Placebo (N=76)	+0.18	---	+2	---
		GLYSET 25 mg t.i.d. (N=74)	-0.08	-0.26	-33	-35†
		GLYSET 50 mg t.i.d. (N=77)	-0.22	-0.40	-45	-47†
		GLYSET 100 mg t.i.d. (N=56)	-0.63	-0.81†	-62	-64†
		GLYSET 200 mg t.i.d. (N=46)	-0.84	-1.02†	-85	-87†
24	4 (non-US) (0288)	Placebo (N=106)	+0.01	---	+8	---
		GLYSET 50 mg t.i.d. (N=117)	-0.35	-0.36†	-20	-28†
		GLYSET 100 mg t.i.d. (N=111)	-0.57	-0.58†	-25	-33†
24	5 (non-US) (0307)	Placebo (N=42)	+0.32	---	+17	---
		GLYSET 100 mg t.i.d. (N=40)	-0.43	-0.75†	-38	-55†

* Mean baseline ranged from 7.54 to 8.72 % in these studies.

**The result of subtracting the placebo group average.

† p ≤ 0.05

Table 2
 GLYSET Plus Sulfonylurea Combination Therapy Results

WEEKS	Study	Treatment	HbA1c (%)		1-hour Postprandial Glucose (mg/dL)	
			Mean Change from Baseline*	Treatment Effect**	Mean Change from Baseline	Treatment Effect**
14	1 (US) D97-057 (0296)	Placebo (N=56)	+0.33	---	-1	--
		GLYSET 50 mg t.i.d. (N=56)	-0.49	-0.82 [†]	-69	-68 [†]
		GLYSET 100 mg t.i.d. (N=57)	-0.41	-0.74 [†]	-73	-72 [†]
52	2 (US) D92-006 (0314)	Placebo (N=93)	+1.01	---	48	--
		GLYSET 25 mg t.i.d. (N=84)	+0.71	-0.30 [†]	-2	-50 [†]
		GLYSET 50 mg t.i.d. (N=89)	+0.39	-0.62 [†]	-13	-61 [†]
		GLYSET 100 mg t.i.d. (N=80)	+0.28	-0.73 [†]	-33	-81 [†]
24	3 (non-US) (0306)	Placebo (N=43)	+0.16	---	+10	--
		GLYSET 100 mg t.i.d. (N=48)	-0.50	-0.66 [†]	-35	-46 [†]

* Mean baseline ranged from 8.56 to 9.16 % in these studies.

** The result of subtracting the placebo group average.

[†]p ≤ 0.05

**Statistical Review and Evaluation
(Carcinogenicity Review)**

NDA: 20-682

APPLICANT: Bayer Pharmaceutical Division

NAME OF DRUG: Glyset (miglitol) Tablets

DOCUMENTS REVIEWED: Vol. 1.1 dated June 6, 1996.
Data on floppy diskettes supplied by the sponsor.

REVIEWING PHARMACOLOGIST: Dr. Herman Rhee

I. BACKGROUND

In this NDA submission, two animal carcinogenicity studies (02232 in mice and 02231 in rats) were included. These two studies were conducted to investigate the carcinogenic potential of miglitol in mice and rats when administered in the diet at some selected dose levels. The mouse study was conducted over 21 months whereas the rat study was conducted over 24 months.

II. THE MOUSE STUDY 02232

IIa. Design

Two separate experiments, one in male and one in female mice, were conducted. In these two experiments, there were three treated groups (known as low, medium and high dose groups) and one control group. The dose levels for treated groups were 200 ppm, 600 ppm and 1800 ppm for low, medium and high dose groups. The dose level for control group was 0 ppm. NMRI mice (50/sex/group) were administered miglitol in the feed for 21 months.

IIb. Reviewer's Analysis

This reviewer independently performed analyses on the survival and the tumor data provided by the sponsor on a floppy diskette. For survival data analysis, methods described in the paper by Cox(1972) and of Gehan (1965) were used. The tumor data were analyzed using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test developed by the Division of Biometrics. The results are included in the Appendix.

Survival Analysis: The purpose of the survival analysis was two-fold:

- (1) To examine the differences in the survival distributions among different dose groups (referred to as the test of homogeneity), and
- (2) To determine the significance of positive linear trend in proportions of deaths with respect to dose levels (called the test of linear trend).

For the theoretical background of these analyses, please refer to Lin et al.(1994) and Thomas et al. (1976).

The following results for survival analysis are contained in the Appendix:

- Tables 1a and 1b summarize the intercurrent mortality data for the male and female mice respectively. No trend or pattern is evident for either male or female mice.
- Figures 1a and 1b depict the Kaplan-Meier survival distributions for males and females respectively. For female mice, the curves for different dose groups intertwine each other suggesting that there is no significant difference between their survival patterns. But for male mice, there appears to be an increased mortality in the medium and high dose groups when compared to the other doses. The test of homogeneity does not yield significant results (Table 2).
- Table 2 describes the p-values of the test of homogeneity and of positive linear trends for males and females using the Cox test and the generalized Kruskal-Wallis test. It is well known that the Kruskal-Wallis test gives more weight to early differences in death rates between groups than the Cox test. None of these tests are significant.

Tumor Analysis: The tumor data analysis was performed to detect, for a selected tumor type in a selected organ/tissue, the significance of positive linear trend in the proportions of discovered tumors with respect to dose levels. The tumor types were classified as fatal and non-fatal.

Following Peto et al. (1980), this reviewer applied the death-rate method and the prevalence method to fatal and non-fatal tumors respectively. For tumors that caused deaths for some, but not all animals, a combined analysis was performed. The exact permutation trend test was used to calculate the p-values of all trend tests, except when the tumor was found in both categories, in which case the continuity corrected normal test was used. The scores used were 0, 200, 600 and 1800 for control, low, medium and high dose groups respectively. This was done in order to reflect the actual dose levels of 0, 200, 600 and 1800 ppm of miglitol. The time-intervals used were 0-52, 53-78, 79-89, 90 and beyond for males and females.

The results for tumor analysis are contained in the Appendix. Tables 3a and 3b describe the p-values for the test of trend based on the tumor data. The rule proposed by Haseman (1983) could be used to adjust for the effect of multiple testings in pairwise comparisons. A similar rule proposed by Lin and Rahman (1995) for trend tests was used in this review. This rule for trend tests says that in order to keep the false-positive rate at the nominal level of approximately 0.1, tumor types with a spontaneous tumor rate of 1% or less (rare tumors) should be tested at a 0.025 significance level, otherwise (for common tumors) a 0.005 significance level should be used.

On the basis of the rule for trend tests described above, no statistically significant positive linear trend or increased incidence was detected in any of the tested tumor types.

III. THE RAT STUDY 02231

IIIa. Design

Two separate experiments, one in male and one in female rats, were conducted. In these two experiments, there were three treated groups (known as low, medium and high dose groups) and one control group. The dose levels for treated groups were 120 ppm, 360 ppm and 1000 ppm for low, medium and high dose groups. The dose level for control group was 0 ppm. Fifty WISW (SPF cpb) Wistar rats/sex/group were administered miglitol in the feed for 24 months.

IIIb. Reviewer's Analysis

This reviewer independently performed analyses on the survival and the tumor data provided by the sponsor on a floppy diskette. For survival data analysis, methods described in the paper by Cox(1972) and of Gehan (1965) were used. The tumor data were analyzed using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test developed by the Division of Biometrics. These results are included in the Appendix.

Survival Analysis: The purpose of the survival analysis was two-fold:

- (1) To examine the differences in the survival distributions among different dose groups (referred to as the test of homogeneity), and
- (2) To determine the significance of positive linear trend in proportions of deaths with respect to dose levels (called the test of linear trend).

For the theoretical background of these analyses, please refer to Lin et al.(1994) and Thomas et al. (1976).

The following results for survival analysis are contained in the Appendix:

- Tables 4a and 4b summarize the intercurrent mortality data for the male and female rats respectively. No trend or pattern is evident.
- Figures 2a and 2b depict the Kaplan-Meier survival distributions for males and females respectively. There appears to be an increased mortality in the medium and high dose groups when compared to the low dose of miglitol. But, the test of homogeneity does not yield significant results (Table 5).
- Table 5 describes the p-values of the test of homogeneity and of positive linear trends for males and females using the Cox test and the generalized Kruskal-Wallis test. It is well known that the Kruskal-Wallis test gives more weight to early differences in death rates between groups than the Cox test. None of these tests are significant.

Tumor Analysis: The tumor data analysis was performed to detect, for a selected tumor type in a selected organ/tissue, the significance of positive linear trend in the proportions of discovered tumors with respect to dose levels. The tumor types were classified as fatal and non-fatal.

According to Peto et al (1980), this reviewer applied the death-rate method and the prevalence method to fatal and non-fatal tumors respectively. For tumors that caused deaths for some, but not all animals, a combined analysis was performed. The exact permutation trend test was used to calculate the p-values of all trend tests, except when the tumor was found in both categories, in which case the continuity corrected normal test was used. The scores used were 0, 120, 360 and 1000 for control, low, medium and high dose groups respectively. This was done in order to reflect the actual dose levels of 0, 120, 360 and 1000 ppm of miglitol. The time-intervals used were 0-52, 53-78, 79-93, 94-103, 104 and beyond.

The results for tumor analysis are contained in the Appendix. Tables 6a and 6b describe the p-values for the test of trend based on the tumor data. The rule proposed by Haseman (1983) could be used to adjust for the effect of multiple testings in pairwise comparisons. A similar rule proposed by Lin and Rahman (1995) for trend tests was used in this review. This rule for trend tests says that in order to keep the false-positive rate at the nominal level of approximately 0.1, tumor types with a spontaneous tumor rate of 1% or less (rare tumors) should be tested at a 0.025 significance level, otherwise (for common tumors) a 0.005 significance level should be used.

On the basis of the rule for trend tests described above, no statistically significant positive linear trend or increased incidence was detected in any of the tested tumor types.

IV. EVALUATION OF VALIDITY OF THE DESIGNS OF THE TWO STUDIES

The reviewer's analyses show that for both studies, there is no statistically significant positive linear trend. However, before drawing the conclusion that the drug is not carcinogenic in mice/rats, it is important to look into the following two issues as having been pointed out by Haseman(1984) in Environmental Health Perspectives:

- (i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumor ?
- (ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals ?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by experts in this field:

- (i) Haseman (1985) has done an investigation on the first issue. He gathered data from 21 studies using Fisher 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on average, approximately 50% of the animals in the high dose group survived the two-year study period.
- (ii) Also, in a personal communication with Dr. Karl Lin of Division of Biometrics II, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be considered as a sufficient number and adequate exposure.
- (iii) In addition, Chu, Cueto and Ward (1981) suggested that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy:

- (i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."
- (ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."
- (iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the two carcinogenicity studies in the light of the above guidelines.

IVa. The Mouse Study 02232

Tables 7a and 7b contain summary survival rates for male and female mice for all the dose levels and for the times: end of 52 weeks, end of 78 weeks and end of 89 weeks. From the survival criteria mentioned above, it can be concluded that enough numbers of mice were exposed to the drug for sufficient amount of time in both sexes.

The reviewing pharmacologist, Dr. Herman Rhee, in his review of pharmacology and toxicology data stated that body weights for high-dose males were about 10% lower than controls throughout the study and the effects in females were less pronounced. From the weight gain criteria mentioned above, it can be concluded that the high dose used may be the maximum tolerated dose for the both sexes. However, to draw any final conclusion in this regard all clinical signs and histopathological effects must be taken into consideration.

IVb. The Rat Study 02231

Tables 8a and 8b contain summary survival rates for male and female rats for all the dose levels and for the times: end of 52 weeks, end of 78 weeks, end of 93 weeks and end of 103 weeks. From the survival criteria mentioned above, it can be concluded that enough numbers of mice were exposed to the drug for sufficient amount of time in both sexes.

The reviewing pharmacologist, Dr. Herman Rhee, in his review of pharmacology and toxicology data stated that under 1000 ppm the growth rates in the males were retarded by 10-15% over the whole course of the study compared to the controls. He further stated that similar observations were noted in the females. From the weight gain criteria mentioned above, it can be concluded that the high dose used may be the maximum tolerated dose for the both sexes. However, to draw any final conclusion in this regard all clinical signs and histopathological effects must be taken into consideration.

V. SUMMARY

Mouse Study 02232:

No statistically significant positive linear trend or increased mortality in the treated groups when compared with the control was detected in either sex.

None of the tested tumor types showed any statistically significant positive linear trend or increased incidence in the treated groups when compared with the control.

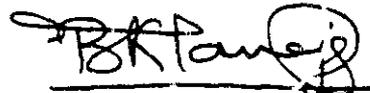
From the survival criteria, it can be concluded that enough numbers of mice were exposed to the drug for sufficient amount of time in both sexes. From the weight gain criteria, it can be concluded that the high dose used may be the maximum tolerated dose for the both sexes. However, to draw any final conclusion in this regard all clinical signs and histopathological effects must be taken into consideration.

Rat Study 02231:

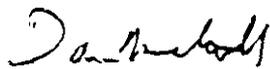
No statistically significant positive linear trend or increased mortality in the treated groups when compared with the control was detected in either sex.

None of the tested tumor types showed any statistically significant positive linear trend or increased incidence in the treated groups when compared with the control.

From the survival criteria, it can be concluded that enough numbers of mice were exposed to the drug for sufficient amount of time in both sexes. From the weight gain criteria, it can be concluded that the high dose used may be the maximum tolerated dose for the both sexes. However, to draw any final conclusion in this regard all clinical signs and histopathological effects must be taken into consideration.



Baldeo K. Taneja, Ph.D.
Mathematical Statistician (Biomed)



Concur: Mr. Marticello

Dr. Lin K.L. 8/29/96

cc: Archival NDA 20-682
HFD-510/Rhee, CSO, Division File
HFD-715/Taneja, Marticello, Lin, Nevius, Division File, Chron.

APPENDIX

Table 1a

Intercurrent Mortality Rates

Animal Type: MOUSE

Sex: MALE

Time (wks)	Dose											
	Conl			Low			Med			High		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
0-52	4	50	8.0	.	.	.	6	50	12.0	3	50	6.0
53-78	5	46	18.0	5	50	10.0	5	44	22.0	4	47	14.0
79-89	8	41	34.0	5	45	20.0	4	39	30.0	8	43	30.0
FNL RILL	33	50	66.0	40	50	80.0	35	50	70.0	35	50	70.0

Source: Bayer Corporation (mouse study)

Table 1b

Intercurrent Mortality Rates

Animal Type: MOUSE

Sex: FEMALE

Time(wks)	Dose											
	Ctrl			Low			Med			High		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
0-52	6	50	12.0	7	50	14.0	8	50	16.0	8	50	16.0
53-78	13	44	38.0	7	43	28.0	12	42	40.0	5	42	26.0
79-89	8	31	54.0	13	36	54.0	5	30	50.0	12	37	50.0
PNL KILL	23	50	46.0	23	50	46.0	25	50	50.0	25	50	50.0

Source: Bayer Corporation (mouse study)

Table 2

ANIMAL: MOUSE

TEST OF HOMOGENEITY

SEX	METHOD	p-value
Male	Cox	0.3674
	Kruskal-Wallis	0.3662
Female	Cox	0.9769
	Kruskal-Wallis	0.9412

TEST OF LINEAR TREND

SEX	METHOD	p-value
Male	Cox	0.6697
	Kruskal-Wallis	0.5836
Female	Cox	0.9930
	Kruskal-Wallis	0.9799

NDA 20-682

2 OF 2

Table 3a

Test of Trend Based on the Tumor Data

Animal Type: MOUSE

Sex: MALE

Organ Name	Tumor Name	Tumor Type	Exact p	Asymp p	#Incid /Ctris	Dose 200	Dose 600	Dose 1600
LIVER	HEPATOCELLULAR ADENOMA	S-	0.9863	(0.9225)	2/50	1	0	0
LIVER	HEPATOCELLULAR CARCINOMA	S-	0.4714	(0.4536)	1/50	3	0	2
LIVER	MALIGNANT HAEMANGIOENDOTH	S-	0.9392	(0.8596)	1/50	1	0	0
PANCREAS	ISLET CELL ADENOMA	S-	1.0000	(0.8240)	1/50	0	0	0
KIDNEYS	CARCINOMA, RENAL CORTEX	S-	0.2448	(0.0473)	0/50	0	0	1
TESTES	LEYDIG CELL TUMOUR	S-	0.8903	(0.8682)	2/50	0	1	0
THYROID GLAND	FOLLICLE CELL ADENOMA	S-	0.7412	(0.7597)	1/50	0	1	0
THYROID GLAND	FOLLICLE CELL CARCINOMA	S-	0.3171	(0.2324)	0/50	1	0	1
ADRENAL GLANDS	CORTICAL ADENOMA	S-	0.6358	(0.6721)	0/50	1	2	0
HEMOLYMPHORET. SYS.	MALIGNANT HISTIOCYTOMA	S-	0.2448	(0.0473)	0/50	0	0	1
HEMOLYMPHORET. SYS.	MALIGNANT LYMPHOMA	S-	0.6663	(0.6645)	4/50	4	3	3
HARDERIAN GLANDS	ADENOMA	S-	0.8567	(0.8487)	4/50	2	7	1
EARS	MALIGNANT HISTIOCYTOMA	S-	0.4800	(0.5580)	0/50	0	1	0
EARS	UNDIFFERENTIATED SARCOMA	S-	0.4896	(0.5253)	0/50	0	1	0
TAIL	FIBROSARCOMA	S-	0.9496	(0.9270)	2/50	2	1	0
TAIL	POORLY DIFFERENTIATED SAR	S-	0.2448	(0.0473)	0/50	0	0	1
		S-	0.7434	(0.7404)	13/50	15	8	10

Note: Tumor Type-M indicates that the tumor is fatal to some but not all animals. Tumor Type-S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.

A '-' indicates a non-significant linear dose-tumor trend.

Source: Bayer Corporation (mouse study)

Table 3a (Continued)

Test of Trend Based on the Tumor Data

Animal Type: MOUSE

Sex: MALE

S-	0.7434	(0.7404)	3/50	3	2	4
S-	0.7434	(0.7404)	0/50	1	0	0

Note: Tumor Type-M indicates that the tumor is fatal to some but not all animals. Tumor Type-S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.

A '-' indicates a non-significant linear dose-tumor trend.

Source: Bayer Corporation (mouse study)

Table 3b

Test of Trend Based on the Tumor Data

Animal Type: MOUSE

Sex: FEMALE

Organ Name	Tumor Name	Tumor Type	Exact p	Asymp p	#Incid /Ctrls	Dose 200	Dose 600	Dose 1800
FORESTOMACH	PAPILLOMA	S-	1.0000	(0.8282)	1/50	0	0	0
LIVER	CAVERNOUS HAEMANGIOMA	S-	0.7895	(0.7526)	0/50	1	0	0
LIVER	HEPATOCELLULAR CARCINOMA	S-	1.0000	(0.8309)	1/50	0	0	0
OVARIES	CYSTADENOMA	S-	1.0000	(0.8309)	1/50	0	0	0
OVARIES	GRANULOSA CELL TUMOUR	S-	0.7843	(0.7783)	3/50	7	3	3
OVARIES	GRANULOSA-THEKA CELL TUMO	S-	0.2604	(0.0545)	0/50	0	0	1
OVARIES	LUTEOMA	S-	0.8481	(0.8520)	1/50	2	2	0
OVARIES	MALIGNANT GRANULOSA CELL	S-	0.0939	(0.0200)	0/50	0	0	2
UTERUS	LEIOMYOMA	S-	0.5208	(0.5589)	0/50	0	2	0
UTERUS	LEIOMYOSARCOMA	S-	0.7226	(0.7596)	1/50	0	2	0
UTERUS	MYOFIBROMA	S-	0.5867	(0.6594)	0/50	1	1	0
UTERUS	MYOMA	S-	0.2604	(0.0545)	0/50	0	0	1
UTERUS	UNDIFFERENTIATED SARCOMA	S-	0.9454	(0.9106)	1/50	2	0	0
PITUITARY GLAND	ADENOMA	S-	0.9222	(0.9130)	0/50	5	1	0
THYROID GLAND	FOLLICLE CELL ADENOMA	S-	0.2604	(0.0545)	0/50	0	0	1
ADRENAL GLANDS	CARCINOMA	S-	0.3289	(0.2544)	0/50	1	0	1
ADRENAL GLANDS	CORTICAL ADENOMA	S-	0.5208	(0.5589)	0/50	0	2	0

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.

A '-' indicates a non-significant linear dose-tumor trend.

Source: Bayer Corporation (mouse study)

Table 3b (Continued)

Test of Trend Based on the Tumor Data

Animal Type: MOUSE

Sex: FEMALE

ADRENAL GLANDS	PHAECHROMOCYTOMA	S-	1.0000	(0.9133)	2/50	0	C	0
HEMOLYMPHORET. SYS.	MALIGNANT LYMPHOMA	S-	0.4851	(0.4777)	20/50	19	18	19
HEMOLYMPHORET. SYS.	MIXED CELL LEUKAEMIA	S-	0.1351	(0.0112)	0/50	0	0	1
HEMOLYMPHORET. SYS.	MYELOID LEUKAEMIA	S-	0.1629	(0.1023)	0/50	0	1	1
SPLEEN	CAVERNOUS HAEMANGIOMA	S-	0.7604	(0.7497)	0/50	1	0	0
HARDERIAN GLANDS	ADENOCARCINOMA	S-	0.9445	(0.8768)	1/50	1	0	0
HARDERIAN GLANDS	ADENOMA	S-	0.2923	(0.2877)	1/50	3	2	3
HARDERIAN GLANDS	CARCINOMA	S-	1.0000	(0.7943)	1/50	0	0	0
MAMMARY GLAND	ADENOCARCINOMA	S-	0.9532	(0.9260)	1/50	3	0	0
FEMUR	OSTEOSARCOMA	S-	1.0000	(0.7943)	1/50	0	0	0
		S-	0.0501	(0.0439)	5/50	2	5	9
		S-	0.0501	(0.0439)	2/50	2	2	3

Note: Tumor Type-M indicates that the tumor is fatal to some but not all animals. Tumor Type-S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.

A '-' indicates a non-significant linear dose-tumor trend.

Source: Bayer Corporation (mouse study)

Table 4a

Intercurrent Mortality Rates

Animal Type: RAT

Sex: MALE

Time (wks)	Dose											
	Ctrl			Low			Med			High		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
0-52	.	.	.	1	50	2.0	.	.	.	1	50	2.0
53-78	2	50	4.0	2	49	6.0	
79-93	1	48	6.0	.	.	.	2	50	4.0	1	47	8.0
94-103	2	47	10.0	.	.	.	1	48	6.0	3	46	14.0
FNL KILL	45	50	90.0	49	50	98.0	47	50	94.0	43	50	86.0

Source: Beyer Corporation (Rat Study)

Table 4b

Intercurrent Mortality Rates

Animal Type: RAT

Sex: FEMALE

Time(wks)	Dose											
	Ctrl			Low			Med			High		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
0-52	1	50	2.0	2	50	4.0
53-78	1	50	2.0	4	50	8.0	3	49	8.0	7	48	18.0
79-93	4	49	10.0	2	46	12.0	2	46	12.0	2	41	22.0
94-103	4	45	10.0	2	44	16.0	5	44	22.0	3	39	28.0
FNL KILL	41	50	82.0	42	50	84.0	39	50	78.0	36	50	72.0

Source: Bayer Corporation (Rat Study)

Table 5

ANIMAL: RAT

TEST OF HOMOGENEITY

SEX	METHOD	p-value
Male	Cox	0.2632
	Kruskal-Wallis	0.2614
Female	Cox	0.4440
	Kruskal-Wallis	0.3552

TEST OF LINEAR TREND

SEX	METHOD	p-value
Male	Cox	0.3562
	Kruskal-Wallis	0.3549
Female	Cox	0.9584
	Kruskal-Wallis	0.9713

Table 6a

Test of Trend Based on the Tumor Data

Animal Type: RAT

Sex: MALE

Organ Name	Tumor Name	Tumor Type	Exact p	Asymp p	#Incid /Ctrls	Dose 120	Dose 360	Dose 1000
		S-	0.4869	(0.4702)	0/50	0	0	1
		S-	0.4869	(0.4702)	0/50	0	1	0
GLANDULAR STOMACH	LEIOMYOSARCOMA	S-	0.4891	(0.4980)	0/50	0	1	0
LIVER	HEPATOCELLULAR ADENOMA	S-	0.2988	(0.2240)	0/50	1	0	1
		S-	0.4869	(0.4702)	0/50	0	1	0
PANCREAS	ADENOCARCINOMA	S-	0.4891	(0.4980)	0/50	0	1	0
PANCREAS	ISLET-CELL ADENOMA	S-	0.0536	(0.0080)	0/50	0	0	2
TESTES	LEYDIG-CELL TUMOR	S-	0.3082	(0.3130)	7/50	5	3	7
TESTES	MESOTHELIOM., MALIGNANT	S-	0.4891	(0.4980)	0/50	0	1	0
SEMINAL VESICLES	ADENOCARCINOMA	S-	0.4891	(0.4980)	0/50	0	1	0
PITUITARY GLAND	ADENOMA	S-	0.3989	(0.3982)	2/50	8	3	5
PITUITARY GLAND	CARCINOMA	S-	0.0584	(0.0101)	0/50	0	0	2
THYROID GLAND	FOLLICLE-CELL ADENOMA	S-	0.1872	(0.1745)	1/50	2	0	3
THYROID GLAND	MEDULLARY CARCINOMA	S-	0.9680	(0.9610)	8/50	5	4	2
PARATHYROID GLANDS	ADENOMA	S-	0.2500	(0.0570)	0/50	0	0	1
ADRENAL GLANDS	CORTICAL ADENOMA	S-	0.1310	(0.1179)	2/50	1	3	4
ADRENAL GLANDS	PHAECHROMOCYTOMA	S-	0.3976	(0.4068)	3/50	5	1	4

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Source: Bayer Corporation (Rat Study)

Table 6a (Continued)

Test of Trend Based on the Tumor Data

Animal Type: RAT

Sex: MALE

HEMOLYMPHORET. SYS.	LEUKAEMIA	S-	0.4891	(0.4980)	0/50 ^M	0	1	C
HEMOLYMPHORET. SYS.	MALIGNANT LYMPHOMA	S-	0.3668	(0.2266)	1/50	0	0	C
SPLEEN	HAEMANGIOENDOTHELIOMA	S-	1.0000	(0.6284)	1/50	0	0	C
MESENT. LYMPH NODE	HAEMANGIOENDOTHELIOMA	S-	0.4891	(0.4980)	0/50	0	1	C
MESENT. LYMPH NODE	HAEMANGIOMA	S-	0.6185	(0.6208)	2/50	4	3	C
SALIVARY GLAND	FIBROSARCOMA	S-	0.7554	(0.7357)	0/50	1	0	C
HARDERIAN GLANDS	ADENOCARCINOMA	S-	0.2337	(0.0447)	0/50	0	0	C
SKIN	FIBROMA	S-	1.0000	(0.8284)	1/50	0	0	C
SKIN	HISTIOCYTOMA	S-	1.0000	(0.8416)	0/50	1	0	C
SKIN	KERATINIZED PAPILLOMA	S-	0.4891	(0.4980)	0/50	0	1	C
SKIN	KERATOACANTHOMA	S-	0.2337	(0.0447)	0/50	0	0	C
SKIN	MALIGNANT HISTIOCYTIC SAR	S-	0.2337	(0.0447)	0/50	0	0	C
SKIN	MALIGNANT HISTIOCYTOMA	S-	1.0000	(0.8416)	1/50	0	0	C
SKIN	SMALL-CELL SARCOMA	S-	0.5000	(0.1676)	0/50	0	0	C
BONE	OSTEOSARCOMA	S-	1.0000	(0.8939)	1/50	0	0	C
		S-	0.4869	(0.4702)	0/50	1	0	C

Note: Tumor Type-M indicates that the tumor is fatal to some but not all animals. Tumor Type-S indicates that the tumor is either fatal or non-fatal to all animals.

A⁺ indicates a significant linear dose-tumor trend.
A⁻ indicates a non-significant linear dose-tumor trend.

Source: Bayer Corporation (Rat Study)

Table 6b

Test of Trend Based on the Tumor Data

Animal Type: RAT

Sex: FEMALE

Organ Name	Tumor Name	Tumor Type	Exact p	Asymp p	#Incid /Ctrls	Dose 120	Dose 360	Dose 1000
		S-	0.1642	(0.1067)	0/50	0	1	0
FORESTOMACH	PAPILLOMA	S-	0.4747	(0.4885)	0/50	0	1	0
LIVER	HEPATOCELLULAR ADENOMA	S-	0.4747	(0.4885)	0/50	0	1	0
PANCREAS	ISLET-CELL ADENOMA	S-	0.7405	(0.7283)	0/50	1	0	0
PANCREAS	ISLET-CELL CARCINOMA	S-	0.2278	(0.0421)	0/50	0	0	1
KIDNEYS	NEPHROBLASTOMA	S-	1.0000	(0.9166)	1/50	0	0	0
		S-	0.1642	(0.1067)	0/50	0	0	1
OVARIES	GRANULOSA THEKA-CELL TUMO	S-	1.0000	(0.9054)	2/50	0	0	0
OVARIES	GRANULOSA-CELL TUMOUR	S-	0.4049	(0.2848)	1/50	0	0	1
OVARIES	MALIGNANT GRANULOSA THEKA	S-	1.0000	(0.8228)	1/50	0	0	0
OVARIES	MALIGNANT SERTOLI-CELL TU	S-	1.0000	(0.8228)	1/50	0	0	0
UTERUS	ADENOCARCINOMA	S-	0.8932	(0.8830)	4/50	2	2	1
UTERUS	ENDOMETRIAL SARCOMA	S-	0.6667	(0.6954)	0/50	0	1	0
UTERUS	FIBROMA	S-	0.2278	(0.0421)	0/50	0	0	1
UTERUS	KERATINIZED SQUAMOUS CELL	S-	0.6668	(0.6632)	1/50	0	3	0
UTERUS	LEIOMYOSARCOMA	S-	1.0000	(0.8228)	1/50	0	0	0
PITUITARY GLAND	ADENOMA	S-	0.1473	(0.1457)	12/50	10	8	14

Note: Tumor Type-M indicates that the tumor is fatal to some but not all animals. Tumor Type-S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Source: Bayer Corporation (Rat Study)

Table 6b (Continued)

Test of Trend Based on the Tumor Data

Animal Type: RAT

Sex: FEMALE

PITUITARY GLAND	CARCINOMA	S-	0.7924	(0.7866)	2/50	4	1	1
THYROID GLAND	FOLLICLE-CELL ADENOMA	S-	0.7405	(0.7283)	0/50	1	0	0
THYROID GLAND	MEDULLARY CARCINOMA	S-	0.0970	(0.0813)	1/50	1	3	3
PARATHYROID GLANDS	ADENOMA	S-	0.9338	(0.8615)	1/50	1	0	0
ADRENAL GLANDS	CORTICAL ADENOMA	S-	0.0770	(0.0706)	4/50	1	0	5
ADRENAL GLANDS	PHAECHROMOCYTOMA	S-	0.2159	(0.1697)	1/50	0	1	2
HEMOLYMPHORET. SYS.	MALIGNANT LYMPHOMA	S-	0.7405	(0.7283)	0/50	1	0	0
SPLEEN	RETICULOSARCOMA	S-	1.0000	(0.8228)	1/50	0	0	0
THYMUS	THYMOMA	S-	0.4747	(0.4885)	0/50	0	1	0
MESENT. LYMPH NODE	HAEMANGIOMA	S-	0.5564	(0.5286)	2/50	0	0	1
HARDERIAN GLANDS	ADENOMA	S-	1.0000	(0.8228)	1/50	0	0	0
HARDERIAN GLANDS	CARCINOMA	S-	1.0000	(0.8228)	1/50	0	0	0
MAMMARY GLAND	ADENOCARCINOMA	S-	1.0000	(0.8385)	1/50	0	0	0
MAMMARY GLAND	FIBROADENOMA	S-	0.5950	(0.5947)	2/50	5	3	3
SKIN	MALIGNANT NEURINOMA	S-	0.2000	(0.0306)	0/50	0	0	1
SKIN	MALIGNANT SCHWANNOMA	S-	1.0000	(0.8385)	1/50	0	0	0

Note: Tumor Type-W indicates that the tumor is fatal to some but not all animals. Tumor Type-S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.

A '-' indicates a non-significant linear dose-tumor trend.

Source: Bayer Corporation (Rat Study)

Table 7a

Survival Rates

Animal: MOUSE

Sex: MALE

Dose	Time (wks)					
	0-52		53-78		79-89	
	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival
Ctrl	46	92.0	41	82.0	33	66.0
Low	.	.	45	90.0	40	80.0
Med	44	88.0	39	78.0	35	70.0
High	47	94.0	43	86.0	35	70.0

Source: Bayer Corporation (mouse study)

Table 7b

Survival Rates

Animal: MOUSE

Sex: FEMALE

Dose	Time (wks)					
	0-52		53-78		79-89	
	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival
Ctrl	44	88.0	31	62.0	23	46.0
Low	43	86.0	36	72.0	23	46.0
Med	42	84.0	30	60.0	25	50.0
High	42	84.0	37	74.0	25	50.0

Source: Bayer Corporation (mouse study)

Table 8a

Survival Rates

Animal: RAT

Sex: MALE

	Time (wks)							
	0-52		53-78		79-93		94-103	
	No. Still Alive	Pct Survival						
Dose:								
Ctrl	.	.	48	96.0	47	94.0	45	90.0
Low	49	98.0
Med	48	96.0	47	94.0
High	49	98.0	47	94.0	46	92.0	43	86.0

Source: Bayer Corporation (Rat Study)

Table 8b

Survival Rates

Animal: RAT

Sex: FEMALE

	Time (wks)							
	0-52		53-78		79-93		94-103	
	No. Still Alive	Pct Survival						
Dose								
Ctrl	.	.	49	98.0	45	90.0	41	82.0
Low	.	.	46	92.0	44	88.0	42	84.0
Med	49	98.0	46	92.0	44	88.0	39	78.0
High	48	96.0	41	82.0	39	78.0	36	72.0

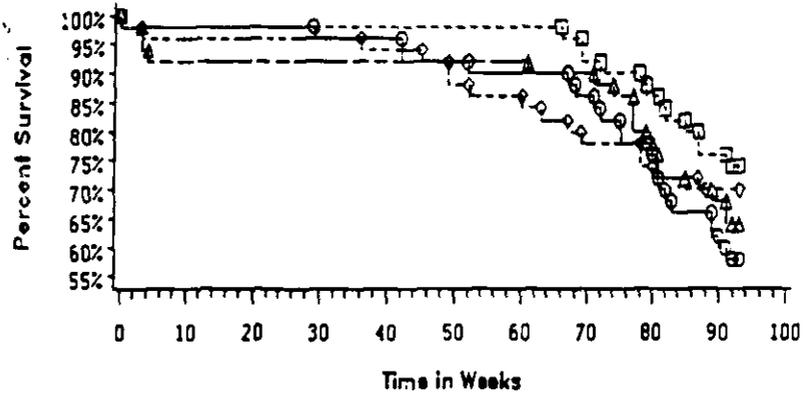
Source: Bayer Corporation (Rat Study)

Figure 1a

Kaplan-Meier Survival Function

Animal: MOUSE

Sex: MALE



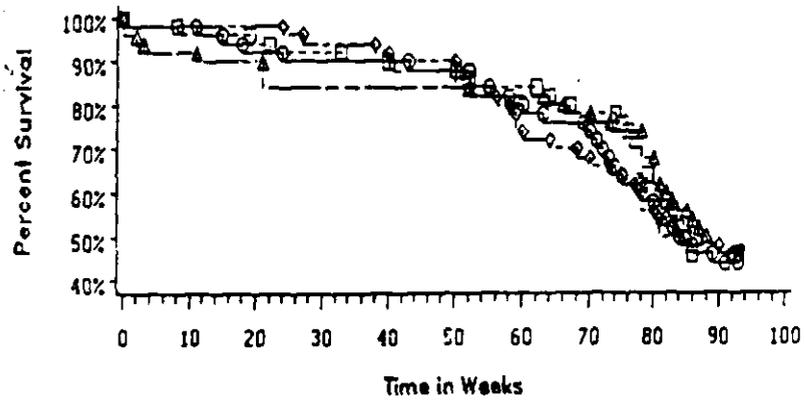
Dose: ○-○-○ Ctrl □-□-□ Low ◇-◇-◇ Med ▲-▲-▲ High

Figure 1b

Kaplan-Meier Survival Function

Animal: MOUSE

Sex: FEMALE



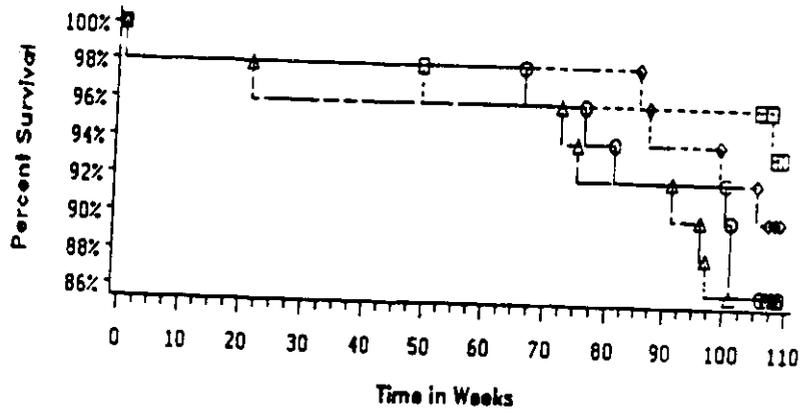
Dose: ○○○ Ctrl □□□ Low ◇◇◇ Med ▲▲▲ High

Figure 2a

Kaplan - Meier Survival Function

Animal: RAT

Sex: MALE



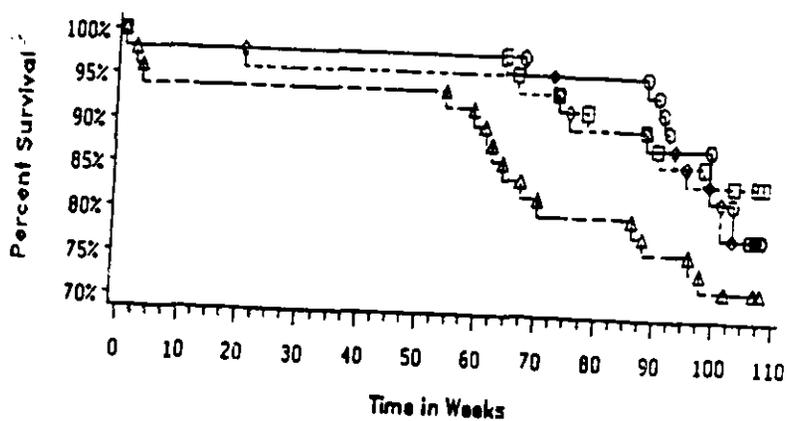
Dose: ○-○-○ Ctrl □-□-□ Low ◇-◇-◇ Med ▲-▲-▲ High

Figure 2b

Kaplan-Meier Survival Function

Animal: RAT

Sex: FEMALE



Dose: ○-○-○ Ctrl □-□-□ Low ◇-◇-◇ Med ▲-▲-▲ High

REFERENCES

1. Chu, Cueto and Ward (1981): Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassay, Journal of Toxicology and Environmental Health, 8, pp. 251-280.
2. Cox (1972): Regression Models and Life Tables, Journal of the Royal Statistical Society, B, 34, pp. 187-220.
3. Gehan (1965): A Generalized Wilcoxon Test for Comparing Arbitrarily Singly Censored Samples, Biometrika, 52, pp. 203-223.
4. Haseman (1983): A reexamination of False Positive Rates for-Carcinogenesis Studies, Fundamental and Applied Toxicology, 3, pp. 334-339.
5. Haseman (1984): Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, Environmental Health Perspectives, 58, pp. 385-392.
6. Haseman (1985): Issues in Carcinogenicity Testing:Dose Selection, Fundamental and Applied Toxicology, 5, pp. 66-78.
7. Lin et al. (1994): Statistical Review and Evaluation of Animal Tumorigenicity Studies. Statistics in Pharmaceutical Industry. Marcel Decker,Inc., pp. 19-57.
8. Lin and Rahman (1995): False Positive Rates in Tests for Linear Trends in Tumor Incidence in Animal Carcinogenicity Studies of New Drug, Unpublished Report, Division of Biometrics, CDER, FDA.
9. Peto et al. (1980): Guidelines for Simple Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments, Long Term and Short Term Screening Assays for Carcinogens: A Critical Appraisal. International Agency for Research Against Cancer Monographs, Supplement 2, World Health Organization, Geneva, pp. 311-426.
10. Sidak (1967): Rectangular Confidence Regions for the Means of Multivariate Normal Distribution, Journal of the American Statistical Association, 62, pp. 626-633.
11. Thomas et al. (1976): Trend and Homogeneity Analyses of Proportions and Life Table Data, Computers and Biomedical Research, pp. 373-387.

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NDA 20-682

June 12, 1996

Sponsor: Bayer Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516

Submission Date: December 28, 1995, Received Jan. 2, 1996

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

Drug Product: Glyset™, Code Name: Bay m 1099
Miglitol 25, 50 and 100 mg tablets

Chemical Name: 3,4,5-Piperidinetriol,1-(2-hydroxyethyl)-2-(hydroxymethyl) - {2R-(2 α ,3 β ,4 α ,5 β)}

Indicated Use: As an adjunctive therapy to diet to lower glucose and glycated hemoglobin in NIDDM patients. Miglitol may also be used in combination with sulfonylureas.

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Herman Rhee, Ph.D.

cc: HFD-510/A Jordan/H Rhee


6/26

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

Drug Product: Glyset™, Code Name: Bay m 1099
Miglitol 25, 50 and 100 mg tablets

Chemical Name: 3,4,5-Piperidinetriol,1-(2-hydroxyethyl)-2-(hydroxymethyl)-{2R-(2 α ,3 β ,4 α ,5 β)}

Indicated Use: As an adjunctive therapy to diet to lower glucose and glycated hemoglobin in NIDDM patients. Miglitol may also be used in combination with sulfonylureas.

Related:

Clinical: Dosage of glyset must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended dose of 100 mg t.i.d.

Pharmacologic category: Brush boarder α -glucosidase inhibitor

I. PHARMACOLOGIC AND PHARMACODYNAMIC STUDIES (Most of all preclinical studies were conducted at the Institute of Toxicology, Industrial Chemicals, Bayer AG, D-5600 Wuppertal, Germany). See of 7/21/1989, of 4/13/1989.

Miglitol is intended for use in the treatment of diabetes mellitus. The application will be focused on the use of miglitol as adjunctive therapy to diet, and in combination with diet and sulfonylureas in NIDDM. Miglitol is a competitive and/or non-competitive inhibitor of α -glucosidase enzymes located on the surface of the brush border of the microvilli. The enzymes are responsible for the hydrolysis of ingested carbohydrates, which increases blood glucose and insulin postprandially. In diabetic patients the postprandial rise in blood glucose is greatly exaggerated due to abnormal insulin secretion and lack of sensitivity to insulin. The inhibition of the intestinal α -glucosidases results in a delay in the hydrolysis of ingested carbohydrates and, consequently, a delay in glucose absorption thereby decreasing the usual postprandial rise in blood glucose levels. However, miglitol will not affect the absorption of ingested monosaccharides such as glucose.

In animal studies miglitol dose-dependently decreased the postprandial rise in both plasma glucose and serum insulin levels when given simultaneously with oral carbohydrate loads. In fasted rats, time dependency for the effect of miglitol on postprandial blood glucose level was studied. Miglitol was most effective when given immediately before or with a carbohydrate meal. Various studies indicate that miglitol did not change the carbohydrate contents of the stomach, small intestine and large intestine of animals given starch or laboratory standard chow.

This suggests that miglitol inhibited the breakdown of carbohydrates without their significant absorption in different animal models. Oral administration of miglitol (0.3-3.0 mg/kg) did not alter the level of hypertriglyceridemia in rats, which suggesting that miglitol does not impede the absorption of triglycerides from the gut.

A single oral doses of miglitol (3-30 mg/kg) had no effect on coagulation, platelet aggregation or fibrolytic activity in rats and miglitol had little or no effects on cardiovascular and respiratory systems. Miglitol (3 - 30 mg/kg) also had no effects on the central nervous system. Similarly, miglitol treatment did not influence neuromuscular transmission in rats. The genitourinary system of rats was evaluated after giving a single oral dose of miglitol (3-30 mg/kg). Miglitol did not change the amount of urine excreted over a 6 h period nor was the urinary concentrations of Na⁺ or K⁺ altered by the drug. Miglitol concentrations ranging from 0.5 mM to 10 mM inhibited the activities of neutral and acid α -glucosidases. After a 17 day treatment period with 10 mM miglitol, glycogen accumulation was found in lysosomes. But, at a therapeutic dose miglitol had no effects on glycogen storage.

When administered to genetically obese, hyperinsulinemic, hyperlipidemic but normoglycemic Zucker rats for 4 weeks, miglitol reduced the body weight gain of the animals in a dose-dependent manner. In obese Zucker rats miglitol reduced the postprandial rise in blood glucose and plasma insulin after 30 to 45 minutes after its treatment in combination with sucrose and/or starch. Miglitol (20-100 mg/100 g diet) for 12 weeks lowered fasting blood glucose levels and urinary glucose excretion in normal and genetically diabetic (db/db) mice. The mechanism of miglitol action is primarily to delay carbohydrate digestion and absorption by the inhibition of sucrase, glucoamylase, isomaltase, lactase, trehalase as the case of acarbose. The K_i values are ranged from 0.1 to 50 μ M. Depending on the diet, the ED_{50} values for miglitol's effect ranged from 0.24 to 0.5 mg/kg in normal animals. Miglitol does not stimulate or enhance insulin secretion and it does not appear to be hypoglycemic like sulfonylureas. But, in human studies it reduce postprandial hyperglycemia which results in reduced glycated hemoglobin levels over time. The most common side effects are flatulence and diarrhea which tend to attenuate with continued therapy.

II. ADME STUDIES (See IND amendment of April 14, 1992)

1. ABSORPTION: In rat miglitol absorption was drug dose-dependent: almost 100% after 1-2 mg/kg, 70% after a 5 mg/kg and 40% after a 25 mg/kg. Administration in food reduced its absorption and saturation of its absorption was noted at higher doses. It appeared that miglitol was absorbed from the upper small intestine and not absorbed from the colon. In many animals

miglitol is well absorbed from the GI tract and the extent of absorption appeared to decrease in dogs, rats and man with increasing doses. The saturability was evident in rats at doses higher than 5 mg/kg, in dogs at doses higher than 20 mg/kg and in humans at doses exceeding 0.7 mg/kg.

2. DISTRIBUTION: Miglitol does not bind extensively to plasma proteins, which was estimated to be under 10% in rat, dog and human. Miglitol is rapidly distributed throughout the body of rats, initially to the extracellular space. Tissue miglitol levels were increased quickly after its administration and reduced rapidly. By 8 hours, in various studies, less than 15% of the administered dose remained in the animal. Significant fraction of miglitol appeared to bind to the intestinal mucosa. In lactating rats miglitol was identified in the milk, whose drug concentration might be higher than that in the plasma.

3. METABOLISM: Miglitol is not metabolized to any measurable extent in rat, dog, or man, which is consistent with the fact that miglitol has no effect on hepatic microsomal enzymes. Biotransformation studies of ^{14}C -miglitol were performed in dogs and rats (Pharm Report#17467), which received orally a single dose (5 mg/kg) of ^{14}C -miglitol (29.85 $\mu\text{Ci}/\text{mg}$) without fasting. A single unchanged drug was identified in the urine of both species. This finding was consistent with the fact that there was no biotransformation product of miglitol.

4. EXCRETION: When ^{14}C -miglitol was administered to rats at 2 and 5 mg/kg, urinary excretions of miglitol were 85 and 41% of the total dose, respectively, which suggests that miglitol's urinary excretion was dose-dependent as the case of its absorption. In dogs, urinary excretion after administration of 2 mg/kg ^{14}C -miglitol by the oral and intravenous routes amounted to 92.3 and 92.6%, respectively. In humans, administration of a 1.4 mg/kg dose by the oral route led to 59% of the administered dose being excreted in the urine. However 96.2% of an intravenously administered dose is excreted in the urine. That is, in various species, the major fraction of miglitol is cleared from the body via the urine and biliary excretion appears to play no role in the elimination of miglitol.

III. PHARMACOKINETIC STUDIES: See amendment of 1/14/91.

1. Pharmacokinetics of ^3H -Miglitol in Male SD Rats (Pharma Report# 10499)

Male SD rats were administered ^3H -miglitol intravenously or orally at dose of 2 mg/kg. The distribution and elimination of miglitol after both IV or oral administration were fast. Oral absorption started rapidly (8 min) and bioavailability was 98.5%. 98.8% of total drug was eliminated renally in 48 hrs after its administration. Drug excretions via the bile and the feces were accounted as 0.15% and 1%, respectively. The renal clearance was

3.7 ml/min and there was no evidence of drug accumulation in organs or tissues.

2. Miglitol Pharmacokinetics: Effects of Dose and Sex (Pharm Report#12929)

Five male SD rats were administered miglitol orally at doses of 1, 5, or 25 mg/kg with a trace of ^3H -Miglitol (62 $\mu\text{Ci}/\text{mg}$). Absorption was 100% at a dose of 1 mg/kg, which was reduced to 70% and 40% at doses of 5 and 25 mg/kg, respectively. Miglitol was uniformly distributed by two phases for most of organs and renal elimination was primarily noted.

3. Summary of Miglitol Pharmacokinetics: After intravenous administration, miglitol was excreted rapidly via the renal route in several species such as in rats, dogs and men. There appears to be no plasma binding fraction of miglitol and elimination half lives are 0.4 - 1.8 hour. After oral administration miglitol was completely absorbed at low doses and a saturation of absorption was evident at or above 5 mg/kg in rats and dogs and at 50 mg in human. Miglitol was distributed in the extracellular space and V_d was low (0.3 - 0.8 l/kg). Miglitol appeared to be not accumulated in tissues. In pregnant rats miglitol crossed the placental barrier slowly and it was also found in milk in lactating rats. The PK data are summarized (Tables 1,2).

IV. TOXICITY STUDIES

1. ACUTE TOXICITY STUDIES (Report#8900) were conducted in the mouse, rats, rabbits and dogs. Potential miglitol toxicity was also studied in various laboratory animals following acute intravenous administration. The top doses for the mouse and rat oral and IV administration were 10,000 mg/kg. The high doses for the rabbit were 10,000 mg/kg for oral and 8,000 mg/kg for IV administration. The oral and intravenous doses for the dogs were 10,000 and 5,000 mg/kg, respectively. There were no toxic signs in mice, but, diarrhea was common 48 hours following dosing in rats, rabbits and dogs. Other toxic signs were labored respiration and reduced motility at high doses (5000 to 10,000 mg/kg).

2. SUBCHRONIC TOXICITY STUDIES (Report#12974): Groups of SPF BOR:NMRI mice (10/sex/group) were administered miglitol in diet at doses of 0, 1000, and 5000 ppm for 3 months. Animal in drug treated groups showed signs of gastrointestinal effects such as soft stool and increase in gas formation in dilated stomach. Mortality was raised in the males after 5000 ppm. There was no treatment-related hematological change or damage in the major organs. Based on the finding, 200, 600, and 1800 ppm were used for the chronic study in mice. Subchronic toxicity studies of one-year duration were also carried out in the rat and dog as listed in table of contents. Animals receiving 4000 ppm (309 mg/kg) had diarrhea from the beginning of the study until week

14. And water consumption was increased for high-dose group animals. Miglitol was well tolerated by females at a dose of 1000 ppm (70 mg/kg) and by males at dose of 250 ppm (17 mg/kg).

3. SUBCHRONIC TOXICITY STUDIES (Report#9425): SPF rats (15/sex/groups) were administered miglitol by gavage once a day at doses of 0, 100, 330 and 1000 mg/kg for 3 months. The clinical signs of treated rats were not differ from the control animals. Nor were any differences in the average amounts of food consumed and the average intakes of water of the treated rats from the controls. The body weight of the rats in the low and medium dose groups was comparable to the control animal. But, the high dose reduced body weight gain after 1 month of the test.

Two animals in the high dose group died of blood accumulation in the lung and liver. The male rats in all treated groups had lower erythrocyte counts as a function of the dose. At the end of the test, the male rats in all treatment groups had more glucose in the plasma than the control males. The absolute weights of liver, spleen and kidney were increased by 12%, 12%, and 9%, respectively in the males. The kidney weight was also increased in female (7%) without effects in other organs. There were no indications that changes in organ weight or histopathological findings were treatment-related.

4. SUBCHRONIC TOXICITY TEST ON BEAGLE DOGS WITH ORAL ADMINISTRATION FOR 13 WEEKS (PHARMA REPORT# 9766A)

A. METHODS: A total 24 pure-bred beagle dogs (weight: 8.3-10.3 kg and the age was 30 to 33 weeks old) were used. The dogs were administered miglitol orally at doses of 0, 50, 150, and 450 mg/kg for 13 weeks.

B. RESULTS:

Mortality: All animals survived for the duration of the study.
Clinical Signs: All treated animals had diarrhea with discolored stool.

Food Consumption: Miglitol had no effect on food consumption.

Body Weight: Control animals gained body weights by 1 kg at the end of the study, while the animals in the low and middle dose groups showed constant weight. The animals in the top dose group showed a slight reduction in weight gain.

Ophthalmoscopic examinations: There was no changes due to the drug-treatment.

Hematology: Miglitol did not cause any hematological changes.

Urinalysis: There were no miglitol treatment-related changes in the parameters.

Gross Pathology: There were no group-specific, dose-dependent pathological findings.

Organ weights: Absolute and relative organ weights in treated animals were not different those from the control animals.

5. CHRONIC 1 YEAR TOXICOLOGICAL STUDIES IN RAT (Report# R4246):

A. METHODS: Twenty SPF Wistar rats/sex/group were administered

miglitol in the feed at doses of 0, 250, 1000, and 4000 ppm for 1 year.

B. RESULTS:

Clinical Signs: There were no remarkable findings in the low and medium dose groups. In the animals of the high dose group, marked diarrhea was observed at the start of the study, which disappeared in the female animals after approximately 14 weeks.

Mortality: 12 rats died: 1-control male; 5-control females; 3-mid-dose females; 3-high dose females. It appears that miglitol treatment had no effect on mortality.

Body Weight: Low dose did not affect the body weight gain of the animals. At 1000 ppm, a temporarily retarded body weight gain was observed in the male animals. The high dose resulted in a marked (approx. 30% for males and 10% for females) retardation of body weight gain as compared to the control animals.

Food and Water Consumption: There were no effects on food consumption in all groups. The water consumption was normal in the low and mid-dose groups. But the high dose resulted in a marked increase (Approx. 90% in males and 47% in females) in water consumption as compared with the control animals.

Ophthalmologic Exam: No apparent drug-related changes.

Hematology: The high dose increased the mean erythrocyte counts and hematocrit at week 52 in both sexes. In the differential blood count in males from the high dose group, the proportion of polymorphonuclear neutrophils was increased slightly as compared with the control values after 3, 6 and 12 months, with the proportion of lymphocytes being slightly decreased.

Clinical Chemistry: Bilirubin concentration was lower than that of the control animals from 6 months after the start of the study onwards for females from the high dose group. Protein concentration was lower at all the investigation times for both males and females of this dosage group. But, these values were within the normal range of historical control values.

Urinalysis: Spurious significant changes for a few parameters at various time periods with no apparent drug-related effects.

Organ Weight: There was no significant and dose-dependent differences in organ weights in all groups. The organ weights in the high dose group, which differed from those of the control animals were likely due to the substantially lower body weight of the animals as compared with the control animal.

Histopathology: The chronic inflammatory cell infiltrated in the liver and local inflammatory cell infiltrated in the parenchyma. This might be regarded as non-specific changes since such changes were also noted in the control animals. There was no treatment-related change in the lung. The small number of neoplastic changes observed in individual rats (mesenchymal kidney tumor in animal#53 in low dose group; Leydig cells tumor in animal#139 of the high dose group)

appeared to be incidental.

6. ONE-YEAR ORAL TOXICITY STUDY IN BEAGLE DOGS (PHARM REPORT#15968)

A. METHODS: Four dogs/sex/group were administered miglitol orally at doses of 0, 20, 60, and 180 mg/kg for a year.

B. RESULTS:

Clinical Signs: Diarrhea was observed in all drug treated animals.

Food Consumption: There was no drug-related effect on food intake.

Body Weight: There was no drug-related effect on body weight gains in all groups.

Ophthalmoscopic findings: There was no treatment-related change.

Neurological Findings: Testing of the reflexes of the animals did not reveal any pathological changes.

ECG Findings: There were no changes in ECG and heart rate in treated animals compared to the control animals.

Hematological Findings: Miglitol had no remarkable effect on hematological parameters.

Clinical Chemistry: The females in the high dose group had an elevation in GOT(10 vs. 16 U/l), which appeared to be treatment-related.

Urinalysis: There were no remarkable findings.

Pathological Findings: At doses of 20 mg/kg upwards the livers of some of the animals appeared yellow in color. Macroscopic investigations did not reveal specifically pathological findings.

Histopathological Findings: There was no histological correlate to the macroscopically found yellowish colorings of the livers of some of the animals. Histological investigations did not reveal any substance-related changes in the organs at any dose.

7. Toxicology Conclusion: Data indicate that miglitol has likely less toxicological complications than Acarbose since the former is not absorbed extensively as the latter.

V. GENOTOXIC STUDIES:

1. Salmonella/Microsomes Test for Point-Mutagenic Effect (Pharm Report# 9659).

A. METHODS: Miglitol was tested for a mutagenic effect in Salmonella/microsomes in doses up to 12,500 µg/plate on strains TA100, TA1537, TA1535, and TA98 in the presence or absence of S-9 mix. The positive agents were Endoxan^R, tryptaflavin and 2-aminoanthracene.

B. RESULTS: Miglitol at doses up to 12,500 µg per plate did not lead to toxic effects on the bacteria without an inhibition of bacterial growth rate. The positive control agents had marked

m colonies.

2. Induction of Induced Forward Mutations in the CHO/HGPRT assay in vitro (Study# T4030777)

A. **METHODS:** Miglitol was evaluated for mutagenic potential at the hypoxanthine-guanine phosphoribosyl transferase locus (forward mutation assay) in CHO cell at doses up to 5000 µg/ml, both with and without S-9 mix. The positive agents were ethylmethanesulfonate and dimethylbenzanthracene.

B. **RESULTS:** Miglitol did not induce dose-related or reproducible increase in mutant frequency above that of the negative controls. The positive agents induced remarkable mutagenic action in the assay system.

3. Micronucleus Test for Mutagenic Effect in the Mouse (Pharm Report# 10864)

A. **METHODS:** To test mutagenic effect of miglitol on the chromosomes of the erythroblasts of the bone marrow, mice were administered orally twice at doses of 4000 and 8000 mg/kg. The dose of endoxan, the positive agent, was 145 mg/kg.

B. **RESULTS:** There was no clear drug effect on erythropoiesis and the ratio of polychromatic to normochromatic erythrocytes. But endoxan had marked mutagenic effect with relevant increase in the polychromatic erythrocytes having micronuclei. Endoxan also inhibited erythropoiesis.

VI. REPRODUCTIVE STUDIES

1. FERTILITY STUDY OF MIGLITOL ON RATS AFTER ORAL ADMINISTRATION (Pharm Report#14225)

A. **METHODS:** Each group had 5-7 weeks old male and 10-11 weeks old female rats (24 males & 60 females Bor:WISW strain). The male rats received miglitol by gavage at doses of 0, 30, 100, or 300 mg/kg for 10 weeks before and during the mating period. The female rats received the same doses of miglitol for 3 weeks before and during the subsequent mating period. Once insemination had taken place (which is day zero of gestation), treatment of the females was continued up to day 7 of gestation.

B. **RESULTS:**

Clinical Signs: The animals treated with doses up to 300 mg/kg showed no specific adverse effects that associated directly with the treatment.

Mortality: A female in the 100 mg/kg group was dead on day 33.

Body Weight: The weight gain in the males was not affected by miglitol at the low- and mid-doses. The mean weight gain of the males in the high dose group was less than that in the control group from the Week 7. There was no effect of miglitol

on weight gain in females in any groups.

Testes Weights: The weight of the testes in the high dose group was greater ($P < 0.05$) than in the control (3.27 ± 0.19 vs. 3.18 ± 0.18 mg/kg).

Macroscopic findings: There were no treatment-related findings.

Insemination, Fertility and Pregnancy: Miglitol had no remarkable effects on male insemination, fertility index, pregnancy index or rearing index.

Reproduction in the caesarean section groups: There was no biologically significant difference between the treated and control groups on mean number of corpora lutea, implantation or fetuses including resorption rate. Likewise, there was no treatment-related changes in mean placental weight, mean fetal weight, and malformations.

Duration of Pregnancy: The dams in all the groups had comparable days of pregnancy.

Implantation: There was no difference in the numbers of implantation sites in the uteri of the animals in all groups (10.1 - 10.8 sites).

2. Investigation for Embryotoxic and Teratogenic Effects in Rats After Oral Administration (Pharm Report# 10195)

A. METHODS: Fifteen inseminated female rats (Bay:FB30)/group were administered miglitol orally by gavage from the 6th to the 15th of pregnancy at doses of 0, 50, 150, or 450 mg/kg. On the 20th day of pregnancy, the females were subjected to caesarean section under ether anesthesia for fetus' examinations.

B. RESULTS:

Dam Mortality: There was no mortality at doses up to 450 mg/kg except a dam whose left chest was filled with a dark blood mass.

Body Weight: The average weight gain in the control group and the treated groups was not different.

Impregnation Rate: Over 95% of inseminated rats became pregnant, with no difference between the control and treated groups.

Embryonal and Fetal Development: In the high dose group, the average fetal weight was reduced. Abnormalities such as cryptorchidism and wavy ribs were noted in a few animals in treated groups as well as in the control.

3. STUDY OF EMBRYOTOXIC EFFECTS OF MIGLITOL IN RABBITS AFTER ORAL ADMINISTRATION (Pharm Report# 14159)

A. METHODS: Fifteen inseminated CHBB:HM rabbits/group were administered miglitol orally at doses of 0, 30, 100, or 300 mg/kg from day 6 to day 18 of gestation.

B. RESULTS:

Mortality of the Dams: One dam in the control group died of general infection.

Weight gain during Gestation: Miglitol reduced weight gain in the

pregnant animals in the 300 mg/kg group.
Insemination and Pregnancy Rate: Please see table below.

Group	#Inseminated	#Fertilized	#Pregnant
Control	15	13	11
30 mg/kg	15	14	10
100 mg/kg	15	14	9
300 mg/kg	15	14	6

Effects of Miglitol on Intrauterine Development: Miglitol treatment had no effects on fetus number per dam or mean body weight of fetus in the low- and the mid-dose groups. But, the high dose reduced the parameters with an increase in malformations (See Table 3), which forced the sponsor repeat another test as described below.

4. DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH ORALLY ADMINISTERED MIGLITOL (Report# MTD9317)

A. **METHODS:** Healthy mature male and female New Zealand White rabbits were used. Twenty inseminated female rabbits/group were administered miglitol orally by gavage at doses of 0, 10, 45, or 200 mg/kg from day 6 through day 18 of gestation.

B. **RESULTS:**

Clinical Signs of the Dams: All animals tolerated miglitol quite well, although there was an increase in soft stool for both the 45 and 200 mg/kg groups.

Body Weight and Food Consumption of the Dams: There was a reduction in mean body weight gain in the 200 mg/kg group. In this group, there was a reduction in food consumption as expected.

Gross Pathology for the Dams: There were no treatment-related pathological findings in any group.

Reproductive Effects: Pregnancy rates, numbers of dams with viable progeny, litter size, numbers of corpora lutea, implantation and/or preimplantation losses, and numbers of resorptions were comparable in 3 treated groups as well as the control.

Observations on Fetuses/Fetal and Placental Weights, Viability and Sex Ratios: Miglitol did not adversely affect placental weight or sex ratio. Morphological development of the placenta appeared to be normal for all groups. But, there was an increase in non-viable fetuses in the 200 mg/kg group (11.5%).

Fetal External and Visceral Examination: There were no treatment-related increases in the incidence of external and/or soft tissue malformations or variations in viable fetuses, although there were a few scattered findings among the 3 treated groups, which the sponsor considered to be of spontaneous origin.

Fetal Skeletal Examination: As expected, based on the reduction in fetal weight, miglitol promoted an increase in the litter incidence of delayed ossification of the fetal skeleton in the high dose group. There was no increase in skeletal malformations for any groups.

Postnatal Development of in the Pups: Live birth index and survival index were not different between the control and the high dose group. The results are in agreement with published data(Ref.#1).

5. PERINATAL AND POSTNATAL TOXIC STUDIES AFTER ORAL ADMINISTRATION IN RATS(Pharm Report# 13248)

A. METHODS: Fifty Bor:WISW female rats/group were mated and administered miglitol by stomach tubes at doses of 0, 30, 100, and 300 mg/kg from the 16th day of gestation up to the end of lactation(21st day after birth).

B. RESULTS:

Mortality of the Dam: There were no deaths in this study.

Dam's Weight Development: Miglitol has no influence on body weight gain except the 100 mg/kg group from day 16 and 20 of gestation. The dose caused weight gain slightly.

Fertility, Pregnancy, Implantation Sites, and Rearing Rate:

Miglitol treatment had no effect on these parameters.

Litter Size: Litter size was not affected by miglitol.

Pups Body Weight: The body weight of the pups was not affected by drug treatment.

6. Postnatal Development of the Young:

Mortality: There was no treatment-related difference in this parameter.

Weight Development: The weight at birth and the weight gain during the 3-week weaning period were comparable in all the groups.

Opening of the Eyes: No significant difference could be found.

Vision and Hearing: There were no impairments of the parameters.

Fertility Test on The F1 Generation: Please see table below.

Investigated Parameters	Control Group	300 mg/kg Group
# of young Dead(%)	0.0	0.2
Alive(Total) (%)	11.4	10.8
Alive(Male) (%)	5.7	5.2
Alive(Female) (%)	5.8	5.7
Weight of the Young(g)	5.29	5.43
Malformed Young(#)	0.0	0.0

7. SUMMARY OF REPRODUCTIVE STUDIES: In a combined male and female fertility study (Segment I), miglitol had no effect on fertility and general reproductive performance in rats after gavage administration of 30, 100, or 300 mg/kg. Himalayan rabbits received miglitol by gavage at doses of 10, 45, or 200 mg/kg. In this study there was no evidence of early counter-gestational effects, but at 200 mg/kg fetal weights were reduced and there was a corresponding increase in delayed ossification of some elements of the fetal skeleton. The effects of orally administered miglitol on perinatal/postnatal development was assessed in the Wistar rat at doses of 30, 100, or 300 mg/kg. This study showed that miglitol increased the incidence of still births at 300 mg/kg, although postnatal development was unaffected. The dose of 300 mg/kg harmed the dams, which caused a reduction in body weight gain and the elevated rate of malformation (Tables 4,5). Treatment of male Wistar rats for 10 weeks before mating and during the 3-week mating period, and treatment of female Wistar rats for up to 6 weeks had no effect on fertility or reproductive performance.

VI. CARCINOGENIC STUDIES

1. CHRONIC and CARCINOGENICITY STUDIES (Report#16640):

A. METHODS: NMRI mice (60/sex/group) were administered miglitol in the feed at doses of 0, 200, 600, and 1800 ppm for 21 months. Ten mice/sex/group were used for interim sacrifice and for the proof of absorption.

B. RESULTS:

Clinical Signs: Reported that none were considered to be remarkable and treatment related.

Mortality: Mortality for males was 35, 23, 30, and 27% for control through high dose males and 48, 47, 45 and 42% for control through high dose females.

Body Weights: The courses for males and females treated with 200 and 600 ppm miglitol corresponded to those for the controls.

Statistically significant differences in these group were only occasional and often had no relationship with the dose. The weights of the males in the 1800 ppm group were about 10% lower than those in the control group. The body weights of the females receiving this dose were similarly reduced, but the effect was less pronounced than in the males.

Food Intake and Test Substance Intake: At week 92 food intake per kg for males was 179, 171, 192 and 212 g/kg/day for control through high dose males and 211, 269, 272, 274 and 282 g/kg/day for control through high dose females. Miglitol intake was 0, 34, 115, and 382 mg/kg/day for control through high dose males and 0, 54, 164, and 507 mg/kg/day for control through high dose females.

Hematology: Mean erythrocyte count: Female -Treated group had slightly lower than that of controls (P(0.05)). Male -There was no significant effect of treatment. Occasionally encountered statistically significant differences in other parameters such

as hemoglobin, hematocrit, or mean corpuscular volume appeared to be no toxicological significance.

Blood Chemistry: Creatinine was reduced in both sexes (37% for male and 26% for female) at high dose at 92 weeks after treatment. Reduction in cholesterol (22%) was noted in male of the high dose group.

Organ Weights: At day 93, the relative spleen and adrenal weights (mg/100 g body weight) were reduced (655 vs 457 in spleen; 35 vs 31 in adrenal) in females of the high dose group. However, the relative weight of kidney was increased from 1323 to 1467 in the group. There was no drug treatment effect in male on organ weights.

Gross Histopathology: Histopathological investigation of the animals of all dose groups intended for interim autopsy after 12 months and those sacrificed at the end of the study yield no evidence of damage by the test substance to the organs investigated. Ulcers and erosions that were discovered in 2 animals and the cause of the increased mortality after 1800 ppm in the first few weeks of the study could not be determined.

Neoplastic Findings (Experimental Pathology Services, Ltd., Hereford, UK, prepared the histological material for examination under Study No. T5016954): Findings in controls were those expected for the age and strain of mice. There were no tumors unusual to this strain of mice in the animals treated with miglitol. The number of neoplasms was not significant. In males blastomas occurred mostly in the lungs, Harder's glands, and reticuloendothelial system (RES). In females, the tumors were largely in the lungs, RES, and the ovaries, which were not miglitol dose-dependent. The number of mice that had different types of tumors are summarized (Table 6).

Harder's glands: Round cell infiltration was present in 22% of the mice. Unilateral adenomas and adenocarcinomas (females only) were found, but their distribution was independent of the dose.

Lungs: Bronchioalveolar neoplasms were common, especially in male mice, which were not drug treatment-dependent. Perivascular and interstitial round cell infiltrations were less frequent.

Ovaries: Frequent findings were cysts (35%), which were found in all groups independently of the treatment.

2. Carcinogenicity Study in Wistar Rats for 2 Years (Report# 18297):

A. METHODS: Sixty WISW (SPF cpb) Wistar rats/sex/group were administered miglitol in the feed at doses of 0, 120, 360, and 1000 ppm for 2 years.

B. RESULTS:

Clinical Signs: Transient diarrhea occurred in 5 males of the 1000 ppm group in the first 29 weeks. There were no other symptoms due to treatment with the test substance.

Mortality: Table below shows the mortality in each group.

Time	0 Month	12 Months	18 Months	24 Months
Death #	Male/Female	Male/Female	Male/Female	Male/Female
Dose 0*	50/50	0/0	2/1	7/11
120	50/50	1/0	1/4	3/ 8
360	50/50	0/1	0/4	5/11
1000	50/50	1/2	3/8	7/14

*Miglitol doses were in parts per million.

Body Weight: The dose of 120 ppm had no effect on the growth rate in males. The dose of 360 ppm delayed growth rates temporarily in males, whilst under 1000 ppm the growth rates in the males were retarded by 10-15% over the whole course of the study compared to the controls. Similar observations were noted in the females.

Feed and Miglitol Intake: Food and water consumption was not remarkably affected by the miglitol. The intake of miglitol was 6.9, 21.1 and 63.2 mg/kg/day in the low, mid, and high dose-groups in males and the intake of miglitol in females was 8.3, 25.7 and 72.4 mg/kg/day in the groups.

Neoplastic Findings:

Total number of tumors and tumor-bearing rats are summarized (Table 7).

Endocrine Organs: The majority of the tumors were found in the endocrine glands such as pituitary adenomas, thyroid tumors, adenomas of the adrenal cortex, pheochromocytomas of the adrenal medulla, and Leydig cell tumor in the testes as characteristic in rats of the age.

Leydig Cells: Total number of benign Leydig cell tumors in the control, low-, med-, and high-dose groups were 11, 6, 5, and 9, respectively.

Lymph Nodes: A total of 14 hemangiomas in the mesenteric lymph nodes were found (11 in males, 3 in females), which were distributed without any dose-dependence among all groups. The type, localization, and number of benign and malignant tumors were not miglitol dose-dependent. The slightly higher total number of tumors and animals with tumors among males in the high dose group was due to higher number of benign tumors, which were still within the relatively wide normal range for Wistar rats (Ref. #2)

Uterus: Hyperemias and polypous hyperplasia of the mucosa were present in many animals in all groups. Adenocarcinomas (group 0 = 4, 1 = 2, 2 = 2, 3 = 1); an endometrial sarcoma (group 2), and a fibroma of the neck of the uterus in a female (group 3) were noted. All other tumors are listed (Tables 7a, b, c).

3. Summaries of Carcinogenicity Studies: In the mouse study, doses of 200, 600, or 1800 ppm (approx. 34, 115, or 382 mg/kg for males and 54, 164, or 507 mg/kg for females) were administered in

the diet daily for 21 months. Body weights for high-dose males were about 10% lower than controls throughout the study; the effects in females were less pronounced. The number of mice with enlarged cecum and colon was also higher in the high-dose group. There were no histopathological changes that could be related to the administration of miglitol at either 12(interim) or 21 month sacrifice and there were no frequency differences in the distribution of either benign or malignant tumors.

In the rat study, doses of 120, 360, or 1000 ppm (approx. 7, 21, or 63 mg/kg for males and 8, 26, or 72 mg/kg for females) were administered in the diet daily for 104 weeks. At 18 months high-dose females had a 16% mortality rate compared to 2% for the control. But, by the end of the study mortality for high-dose females was 28% compared to 22% for controls. Growth for males was retarded over the course of the study at the high dose and was temporarily delayed at the mid-dose. Both males and females from the 1000 ppm group consumed more water than did the control. There was a higher incidence of Leydig cell hyperplasia in high-dose animals vs. controls (13 males from the 1000 ppm group vs 3 from the control). But, there was no dose-dependent distribution of Leydig cell tumors (control 7, 120 ppm 5, 360 ppm 3, 1000 ppm 7). A slightly higher total number of tumors and animals with tumors among high-dose males appeared to be due to higher number of benign tumors (Table 7).

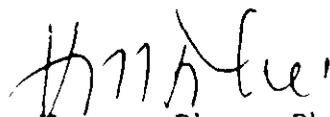
4. The high dose was the maximum tolerated dose according to the sponsor's range-finding study (Bayer Report # 4246, 12/07/1987). In that study male rats receiving 4000 ppm showed a severe growth retardation with body weights about 30% lower than controls. The feeding of 1000 ppm resulted in growth retardation, which was selected as the top dose in the 2 year carcinogenic studies.

VIII. REFERENCES

- 1). Clemens, G.R., Grosso, D.S., Hartnagel, R.E.: Developmental toxicity (Segment II) study in rabbits with orally administered Bay M 1099. R. Report No. 6311, October, 19, 1994.
- 2). E. Bombard et al: J. Environ. Pathol. Toxicol. Oncol. 7:35, 1986).

IX. RECOMMENDATION

Pharmacology recommends approval of miglitol for the proposed indication.


Herman Rhee, Ph.D.

cc: HFD-510/A Jordan/H Rhee

Calculation of Multiple of Human Dose*

Representative surface area to weight ratios (km) for various species are follows:

	<u>Body Weight(kg)</u>	<u>Surface Area(Sq.M.)</u>	<u>km factor</u>
Man	60	1.6	37
Rat	0.15	0.025	5.9
Mouse	0.02	0.0066	3.0

Human: Based on a 60 kg person, Maximum HTD from labelling:
300 mg

$$300 \text{ mg} \div 60 \text{ kg person} = 5 \text{ mg/kg maximum HTD}$$

$$5 \text{ mg/kg} \times 37 \text{ (km factor)} = 185 \text{ mg/m}^2$$

Mouse:

$$270 \text{ mg/kg} \times 3 \text{ (km factor)} = 810 \text{ mg/m}^2$$

Rat:

$$100 \text{ mg/kg} \times 6 \text{ (km factor)} = 600 \text{ mg/m}^2$$

Multiple of max. HTD (300 mg)

Mouse:

$$\text{For } 270 \text{ mg/kg:}$$

$$810 \text{ mg/m}^2 \div 185 \text{ mg/m}^2 = 4.38 \text{ times}$$

Rat:

$$\text{For } 100 \text{ mg/kg:}$$

$$600 \text{ mg/m}^2 \div 185 \text{ mg/m}^2 = 3.24 \text{ times}$$

* Based on Freireich, E. J., et al. Quantitative comparison of toxicity of anticancer agents in mouse, rat, dog, monkey and man. Cancer Chemother. Repts. 50(4):219-244, 1966.

Table 1 Pharmacokinetic parameters of total radioactivity after a single administration of [³H]miglitol (Sprague Dawley-rat, man) or [¹⁴C]miglitol (dog) to different species.

Species	rat		dog		man	
Route	i.v.	p.o.	i.v.	p.o.	i.v.	p.o.
Dose [mg/kg]	5	2	3	2	1.4	1.4
No of individuals	5	5	3	3	6	6
pharmacokinetic parameters (geom. means and deviations)						
t _{1/2} ^a [h]	0.35	-	1.29	-	1.78	-
t _{1/2} [h]	3.36 (1.26)	2.36 (1.78)	4.38 (1.16)	3.57 (1.14)	2.31 (1.22)	2.35 (1.26)
AUD [mg h l ⁻¹]	1.94 (1.08)	1.69 (1.05)	1.07 (1.26)	8.47 (1.28)	12.7 (1.18)	7.82 (1.33)
AUC [mg h l ⁻¹]	2.29 (1.08)	1.76 (1.05)	11.2 (1.24)	8.64 (1.28)	13.6 (1.18)	8.03 (1.34)
AUC _{norm} [h ⁻¹ ·kg ⁻¹]	1.14 (1.08)	0.879 (1.05)	5.62 (1.24)	4.32 (1.28)	9.76 (1.19)	5.76 (1.24)
CL [l·h ⁻¹ ·kg ⁻¹]	0.875 (1.08)	-	0.178 (1.24)	-	0.103 (1.19)	-
V _{ss} [l·kg ⁻¹]	0.83	1.11	0.49 (1.25)	-	0.28 (1.12)	-
C _{max, norm} [h]	-	-	-	1.11 (1.51)	-	-
t _{max} [h]	-	0.67 (1.00)	-	2.88 (1.77)	-	1.13 (1.35)
Time of observation [h]	0.083 - 8	0.17 - 8	0.05 - 24	0.33 - 24	0.083 - 14	0.083 - 14

a) calculated in the first elimination phase up to 2 h (rat) and resp. 8 h (dog, man)

Table 2 Pharmacokinetic parameters of inhibitory activity after single administration of miglitol to male and female beagle dogs in single bolus doses of 20, 60, 180, and 450 mg/kg (cross over). Data represent geometric means and deviations of N = 6 (3 female, 3 male). No sex-differences have been observed.

dose [mg·kg ⁻¹]	20	60	180	450
t _{1/2} [h]	6.68	7.45	4.13	5.33
AUC [mg·h l ⁻¹]	75.9	211	274	580
AUC _{norm} [kg·h l ⁻¹]	3.79	3.52	1.52	1.29
Cl _r [l h ⁻¹ kg ⁻¹]	0.133	0.160	0.182	0.157
C _{max, norm} [kg l ⁻¹]	0.97	0.68	0.29	0.24
t _{max} [h]	1.5	1.6	2.1	1.7

BAYER AG

Table 3

TABLE / TABELLE 5

MEAN VALUES + STANDARD DEV. / DURCHSCHNITTSWERTE + STANDARDABW.

STUDY NO. / STUDIEN-NR. EFFECT OF MAY 1979 / WIRKUNG VON MAY 1979
 14 818 762 ON PREGNANT PATIENTS AND THEIR FETUSES / AN TRAECHTIGEN KANINCHEN UND DEREN FETEN
 13 DAILY TREATMENTS PER OS / 13 TAEGLICHE BEHANDLUNG PER OS
 FROM DAY 6 TO 18 OF PREGNANCY / VON 6. BIS 18. TAG DER TRAECHTIGKEIT

GROUP / GRUPPE	HEIGHT GAIN (G) DURING PREGNANCY / WACHSTUM DER KÖRPERGRÖßE WÄHREND DER TRAECHTIGKEIT		NUMBER (PER DAM) / ANZAHL (PRO MUTTER) DER FETUS		LOSSES / VERLUSTE		MEAN - WEIGHT IN GRAPHS / DURCHSCHNITTL. GEWICHT IN GRAMM DER FETEN		FOETUS MALFORMATIONS / FETUS-VERÄNDERUNGEN		RUMTS	
	TREATMENT / BEHANDLUNG	(G) / (G)	IMPLANT / IMPLANT	MALE / MÄNNL.	FEMALE / FEM.	SUM / GESAMT	DEER / VERLUSTE	FOETUS / FETUS	PLACENT. / PLACENT.	INFORMATIONS / INFORMATIONEN	< 25 GR / < 25 GR	GR / GR
CUNTR.	45.8 113.4	1.6 60.6	6.4 2.6	1.9 1.4	2.0 1.7	4.8 2.6	1.7 2.9	39.40 5.08	4.83 1.10	0.27 0.65	0.0 0.0	0.07 0.38
GRP. 1	105.5 150.5	-15.3 112.1	6.9 1.5	2.4 2.2	1.8 2.0	4.2 3.1	2.0 3.3	39.00 6.15	4.42 0.59	0.18 0.32	0.29 0.42	0.0 0.0
GRP. 2	73.9 157.0	18.9 99.1	6.4 2.3	1.2 1.3	1.6 1.6	2.9 2.6	3.6 3.3	39.56 5.57	4.71 0.62	0.11 0.33	0.22 0.44	0.0 0.0
GRP. 3	-51.3 ^M 112.2	-107.2 ^M 103.5	6.1 2.3	0.6 ^M 1.2	0.7 ^M 1.4	1.4 ^M 2.0	4.8 ^M 3.2	33.07 9.85	4.13 1.22	0.17 0.41	0.58 ^M 0.55	1.00 ^{M*} 1.67

^M) SIGNIFICANT DIFFERENCE TO CONTROL (P < 0.05) / SIGNIFIKANTER UNTERSCHIED ZUR KONTROLLE (P < 0.05)
^{**}) SIGNIFICANT DIFFERENCE TO CONTROL (P < 0.001) / SIGNIFIKANTER UNTERSCHIED ZUR KONTROLLE (P < 0.001)

Table 4

List of all blastomas with allowance for number, localization, type, and status (final autopsy)

Dose (ppm)	0	200	600	1800	0	200	600	1800
Organ/tissue	Males				Females			
Tumour type								
Lungs								
investigated	48	47	46	49	47	49	50	47
Adenoma (b)	13	15	8	10	5	2	5	9
Adenocarcinoma (m)	3	4	2	4	2	2	2	3
Liver								
investigated	48	47	46	48	47	49	50	47
Hepatocellular adenoma (b)	2	1	0	0	0	0	0	0
Hepatocellular carcinoma (m)	1	3	0	2	1	0	0	0
Cavernous haemangioma (b)	0	0	0	0	0	1	0	0
Haemangi endothelioma (m)	1	1	0	0	0	0	0	0
Cardiac stomach								
investigated	48	47	47	49	47	49	50	47
Papilloma (b)	0	0	0	0	1	0	0	0
Pancreas								
investigated	47	47	47	45	46	49	50	46
Islet-cell adenoma (b)	1	0	0	0	0	0	0	0
Spleen								
investigated	48	47	46	48	47	49	50	47
Cavernous haemangioma (b)	0	0	0	0	0	1	0	0
RES								
investigated	48	47	46	48	47	49	50	47
Lymphoma (m)	4	4	3	3	20	19	18	19
Myelocytic leukaemia (m)	0	0	0	0	0	0	1	1
Mixed cell leukaemia (m)	0	0	0	0	0	0	0	1
Histiocytoma (m)	0	0	1	1	0	0	0	0
Bones (femur)								
investigated	47	46	46	49	47	49	50	47
Osteosarcoma (m)	0	0	0	0	1	0	0	0
Harder's glands								
investigated	50	49	48	50	50	50	49	48
Unilateral adenoma (b)	4	2	7	1	1	3	2	3
Unilateral adenocarcinoma (m)	0	0	0	0	2	1	0	0
Pituitary								
investigated	46	48	47	44	47	47	48	48
Adenoma (b)	0	0	0	0	0	5	1	0
Adrenals								
investigated	48	47	46	48	47	49	50	47
Unilateral corticoadenoma (b)	0	1	2	0	0	0	2	0
Unilateral pheochromocytoma (b)	0	0	0	0	2	0	0	0
Unilateral carcinoma (m)	0	0	0	0	0	0	0	1
Bilateral carcinoma (m)	0	0	0	0	0	1	0	0

Table 5

List of all blastomas with allowance for number, localization, type, and status (final autopsy)

Organ/tissue Tumour type	Males				Females			
	0	200	600	1800	0	200	600	1800
Testes								
investigated	48	47	46	49	-	-	-	-
Unilateral Leydig cell tumour (b)	2	0	1	0	-	-	-	-
Mammary glands								
investigated	-	-	-	-	45	49	50	47
Adenocarcinoma (m)	-	-	-	-	1	3	0	0
Ovary								
investigated	-	-	-	-	46	47	50	47
Unilateral luteoma (b)	-	-	-	-	1	1	2	0
Bilateral luteoma (b)	-	-	-	-	0	1	0	0
Cystadenoma (b)	-	-	-	-	1	0	0	0
Unilateral granulosa cell tumour (b)	-	-	-	-	3	6	2	2
Bilateral granulosa cell tumour (b)	-	-	-	-	0	3	1	1
Unilateral granulosa theca cell tumour (b)	-	-	-	-	0	0	0	1
Unilateral granulosa cell tumour (m)	-	-	-	-	0	0	0	2
Uterus								
investigated	-	-	-	-	47	49	50	47
Myoma/leiomyoma/myofibroma (b)	-	-	-	-	0	1	3	1
Leiomyosarcoma (m)	-	-	-	-	1	0	2	0
Undifferentiated sarcoma (m)	-	-	-	-	1	2	0	0
Kidneys								
investigated	48	47	46	49	47	49	50	47
Unilateral corticocarcinoma (m)	0	0	0	1	0	0	0	0
Thyroid								
investigated	48	47	46	49	46	48	49	47
Unilateral follicle cell adenoma (b)	1	0	1	0	0	0	0	1
Unilateral follicle cell carcinoma (m)	0	1	0	1	0	0	0	0
Connective tissue (ear, tail)*								
Undifferentiated sarcoma (m)	0	0	2	1	0	0	0	0
Fibrosarcoma (m)	2	2	0	0	0	0	0	2

*not routine investigated

Table 6 Number of Mice with Benign and/or Malignant Tumors After 21 Months								
	Diet Concentration - ppm							
	Males				Females			
	0	200	600	1800	0	200	600	1800
No. of Mice Evaluated	50	50	49	50	50	50	50	50
No. of Mice with Tumors	26	27	21	22	31	33	31	32
No. of Mice with Benign Tumors Only	16	13	13	10	4	8	9	8
No. of Mice with Malignant Tumors Only	7	9	6	10	18	16	15	16
No. of Mice with Both Benign & Malignant Tumors	3	5	2	2	9	9	7	8

(Data from ref. 3)

Table 7 Total Number of Tumors and Tumor-bearing Animals - Rat Carcinogenicity Study								
	Diet Concentration - ppm							
	Males				Females			
	0	120	360	1000	0	120	360	1000
No. of Animals Examined	50	50	50	50	50	50	50	50
Total No. of Tumors	29	34	26	40	41	27	26	35
Benign Tumors	18	29	15	30	25	19	15	27
Malignant Tumors	11	5	11	10	16	8	11	8
No. of Animals with Tumors	20	27	21	30	30	22	18	26
No. of Animals with Multiple Tumors	7	7	3	9	9	5	5	8
No. of Animals with Benign Tumors Only	9	22	11	20	14	15	8	18
No. of animals with Malignant Tumors Only	7	4	10	6	10	5	7	5
No. of Animals with Benign & Malignant Tumors	4	1	0	4	6	2	3	3

(Data from ref. 6)

Table 7a Number, localization and kind of tumours
(main groups)

Dose (ppm)	0	120	360	1000	0	120	360	1000
Organ/tissue	male rats				female rats			
Brain								
Animals examined	50	50	50	50	50	50	50	50
Medulloblastoma (m)	0	0	0	1	0	0	0	0
Oligodendroglioma (m)	0	0	1	0	0	0	1	0
Pituitary								
Animals examined	50	50	49	48	49	50	49	48
Adenoma (b)	2	6	3	5	12	10	8	14
Carcinoma (m)	0	0	0	2	2	4	1	1
Harderian Gland								
Animals examined	47	49	50	47	49	46	46	41
Adenoma (b) (unilateral)	0	0	0	0	1	0	0	0
Adenocarcinoma (m) (uni.)	0	0	0	1	0	0	0	0
Carcinoma (m) (unilateral)	0	0	0	0	1	0	0	0
Salivary Gland								
Animals examined	50	50	50	50	50	50	50	49
Fibrosarcoma (m)	0	1	0	0	0	0	0	0
Thyroid								
Animals examined	50	50	50	50	50	49	50	48
Follicular adenoma (b) (unilateral)	1	2	0	3	0	1	0	0
medullary Carcinoma (m) (unilateral)	7	5	3	2	1	1	3	3
medullary Carcinoma (m) (bilateral)	1	0	1	0	0	0	0	0
Parathyroids *								
Animals examined	36	38	42	42	31	43	42	40
Adenoma (b) (unilateral)	0	0	0	1	1	1	0	0
Thymus								
Animals examined	45	48	48	47	48	46	47	41
Thymoma (b)	0	0	0	0	0	0	1	0
Lymph Nodes-Mesenteric								
Animals examined	49	50	49	49	50	49	49	48
Haemangioma (b)	2	4	3	2	2	0	0	1
Haemangi endothelioma (b)	0	0	1	0	0	0	0	0
Lungs								
Animals examined	50	49	50	49	50	50	50	49
bronch.-alveolar Adenoma (b)	0	1	0	0	0	0	0	0
Forestomach								
Animals examined	45	49	49	49	47	49	50	49
Papilloma (b)	0	0	0	0	0	0	1	0
Glandular Stomach								
Animals examined	49	50	49	50	50	50	50	49
Leiomyosarcoma (m)	0	0	1	0	0	0	0	0
Liver								
Animals examined	49	50	49	50	50	50	50	49
hepatocellular Adenoma (b)	0	1	0	1	0	0	1	0

Table 7b cont.

Dose (ppm)	0	120	360	1000	0	120	360	1000
Organ/tissue	male rats				female rats			
Spleen								
Animals examined	49	50	49	50	50	50	50	49
Haemangioendothelioma (b)	1	0	0	0	0	0	0	0
Reticulumcell(sarcoma (m)	0	0	0	0	1	0	0	0
Leukaemia (m)	0	0	1	0	0	0	0	0
Pancreas								
Animals examined	49	50	49	49	50	50	50	49
Islet cell adenoma (b)	0	0	0	2	0	1	0	0
Islet cell carcinoma (m)	0	0	0	0	0	0	0	1
Adenocarcinoma (m)	0	0	1	0	0	0	0	0
Kidneys								
Animals examined	49	50	49	50	50	50	50	49
Nephroblastoma (m) (uni.)	0	0	0	0	1	0	0	0
Adrenal cortex								
Animals examined	48	50	46	50	50	50	50	48
Cortical Adenoma (b) (uni.)	2	1	3	4	3	1	0	4
Cortical Adenoma (b) (bil.)	0	0	0	0	0	0	0	1
Adrenal medulla								
Animals examined	48	49	45	50	50	49	47	48
Phaeochromocytoma (b) (unilateral)	3	5	1	4	1	0	0	2
Phaeochromocytoma (b) (bilateral)	0	0	0	0	0	0	1	0
Mammary Gland								
Animals examined	47	49	49	50	49	50	49	49
Fibroadenoma (b)	0	0	0	0	2	5	3	3
Adenocarcinoma (m)	0	0	0	0	1	0	0	0
Testes								
Animals examined	49	50	49	50	-	-	-	-
Leydig cell tumor (b) (uni.)	7	4	3	6	-	-	-	-
Leydig cell tumor (b) (bil.)	0	1	0	1	-	-	-	-
Mesothelioma (b) (uni.)	0	0	1	0	-	-	-	-
Seminal vesicle								
Animals examined	49	50	49	50	-	-	-	-
Adenocarcinoma (m) (uni.)	0	0	1	0	-	-	-	-
Ovaries								
Animals examined	-	-	-	-	50	50	50	49
Granulosa cell tumor (b) (unilateral)	-	-	-	-	1	0	0	1
Granulosa theca cell tumor (b) (unilateral)	-	-	-	-	2	0	0	0
Granulosa theca cell tumor (m) (unilateral)	-	-	-	-	1	0	0	0
Sertoli cell tumor (m) (uni.)	-	-	-	-	1	0	0	0

Table 7 c cont.

Dose (ppm)	0	120	360	1000	0	120	360	1000
Organ/tissue	male rats				female rats			
Uterus								
Animals examined	-	-	-	-	50	50	50	49
Fibroma (b)	-	-	-	-	0	0	0	1
Adenocarcinoma (m)	-	-	-	-	4	2	2	1
Squamous cell carcinoma (m)	-	-	-	-	1	0	3	0
endometrial Sarcoma (m)	-	-	-	-	0	0	1	0
Leiomyosarcoma (m)	-	-	-	-	1	0	0	0
Spinal Cord								
Animals examined	49	50	49	49	50	50	50	49
Astrocytoma (m)	0	0	1	0	0	0	0	0
Sciatic Nerve								
Animals examined	47	50	49	49	50	49	49	49
malignant Neurinoma (m)	0	0	0	0	0	0	0	1
Other Locations*								
Skin / Subcutis								
Squamous Papilloma (b)								
(extremity pelvic)	0	0	1	0	0	0	0	0
Histiocytoma (b) (cheek)	0	1	0	0	0	0	0	0
Keratoacanthoma (b)								
(regio abdominalis)	0	0	0	1	0	0	0	0
small cell Sarcoma (m)								
(inguinal)	0	0	0	1	0	0	0	0
fibrous, histiocytic Sarcoma								
(m) (nose)	0	0	0	1	0	0	0	0
malignant Histiocytoma (m)								
(vault)	1	0	0	0	0	0	0	0
malignant Neurinoma (m)	0	0	0	0	0	0	0	1
malignant Schwannoma (m)	0	0	0	0	1	0	0	0
Bones								
Osteosarcoma (m) (cranium)	1	0	0	0	0	0	0	0
Reticuloendothelial System								
malignant Lymphoma (m)	1	0	0	2	0	1	0	0

* not routinely examined

Clinical Pharmacology and Biopharmaceutics Review

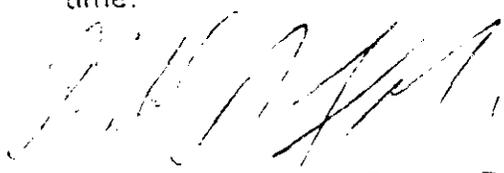
NDA: 20-682
 Miglitol 25, 50, 100 mg
 tablets
 (Glyset) DEC 5 1996
 Submission Date: 11/12/96
 Sponsor: Bayer
 Type of Submission: Minutes of a telecon
 Reviewer: Michael J. Fossler, Pharm. D., Ph. D.

Submission

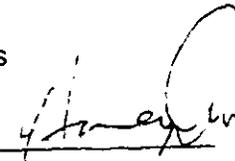
The submission dated 11/12/96 consists of the the firm's minutes of the teleconference between Drs. Hae-Young Ahn, Xavier Ysern and Michael Fossler of the FDA and Drs Garvey, Lettieri and Poirier of Bayer on 11/6/96 concerning the dissolution specification for miglitol tablets. The Agency's minutes have been previously submitted to the file (see memo dated 11/6/96).

Recommendations

After review of the submitted minutes, OCPB feels they are an accurate representation of the teleconference. OCPB has no comments for the firm at this time.

 11/25/96
 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  12/2/96

CC: NDA 20-682 (orig., 1 copy), HFD-510(Rhee), HFD-850(Lesko), HFD-870(M. Chen, Fossler, Ahn, Drug File, Chron. File, Reviewer File), HFD-340 (Vish)
 9/19/96

Minutes of November 6, 1996
Teleconference between Bayer Corporation and FDA,
regarding Miglitol Dissolution Specifications

FDA Participants:

Hae Young Ahn, Ph.D.
Michael Fossler, Ph.D.
Xavier Ysern, Ph.D.

Bayer Participants:

Maureen Garvey, Ph.D.
John Lettieri, Ph.D.
Albert Poirier

This teleconference was arranged at Dr. Fossler's suggestion following:

- Bayer's NDA dissolution specification for miglitol of _____ in 30 minutes
- FDA's September 20, 1996 facsimile suggesting _____ in 20 minutes
- Bayer's October 11, 1996 response proposing _____ in 30 minutes
- October 17, 1996 telephone call from Dr. Fossler suggesting a teleconference to discuss the dissolution specifications for miglitol

Discussion:

Dr. Fossler asked that we use the term "specification" to refer to "Q."

A. Poirier described how Bayer, in response to the FDA September 20, 1996 fax, reviewed the data at 20 minutes to see if we could agree to a specification of _____ at 20 minutes. With this specification, average dissolution data show:

- The 25 mg tablet is almost _____ dissolved.
- The 50 mg tablet is close to _____ dissolved.
- The 100 mg tablet has average dissolution values as low as _____. A Q=_____ would introduce a real potential for batch failure. A. Poirier anticipated that we would have to go to stage II testing 4 out of 5 times.

Minimum dissolution data show:

- _____ for the 25 mg tablet
- _____ for the 50 mg tablet
- _____ for the 100 mg tablet. The frequency for required stage II testing would be higher than is reasonable.

With a specification of _____ at 30 minutes, the 25 mg and 50 mg tablets are essentially dissolved. The 100 mg tablet does not present an unreasonable potential for batch failure or for stage II testing which would be required about 1 out of 5 times.

J. Lettieri described the slow absorption of miglitol which peaks at 2 to 3 hours. Although we do not have data showing an in vitro/in vivo correlation, no effect on absorption is anticipated by a 10 minute difference in dissolution.

Dr. Fossler questioned why a highly soluble drug should require a 30 minute dissolution specification and asked if there was coning during dissolution testing.

A. Poirier responded that there is coning and that is why the speed has been specified at 75 rpm, to help minimize this effect.

Dr. Fossler asked if the phrase "high regulatory exposure" in the October 20, 1996, fax from Bayer referred to FDA field inspectors

A. Poirier answered yes, that a high frequency of stage II testing is viewed as a process that is out of control.

Dr. Fossler said that the Biopharmaceutics group views dissolution testing differently; Biopharmaceutics sets the specification based on stage II testing. Dr. Fossler's preference was for testing 12 tablets instead of 6 and **Dr. Ahn** commented that the goal of stage II testing is to assure that tablets at the upper and lower dissolution limits are bioequivalent.

Conclusion:

Dr. Fossler commented that the Bayer arguments were convincing, although prior to the teleconference, he had a problem reconciling the high solubility of the drug with Bayer's difficulty in meeting a 20 minute specification. FDA will accept the following dissolution specifications:

Q	=
Time	= 30 minutes
Apparatus	= Type II
Speed	= 75 rpm
Medium/Volume	= water/900 mL
Temperature	= 37°C

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-682
Miglitol NOV 8 1996
25, 50, 100 mg tablets
(Glyset[®])
Submission Date: 10/11/96
Sponsor: Bayer, West Haven, CT
Type of Submission: Response to Request for Information
Reviewer: Michael J. Fossler, Pharm. D., Ph. D.

Submission

The submission dated 10/11/96 is for miglitol, indicated for the treatment of non-insulin dependent diabetes mellitus. In the review of the original NDA, OCPB recommended a dissolution specification of Q = in 20 minutes. In the present submission, the firm proposed a specification of Q = in 30 minutes. A teleconference was held between OCPB, ONDC and representatives from Bayer (see attached minutes) in which it was agreed that Q = in 30 minutes would be acceptable. Therefore, no further action is indicated.


11/8/96
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


11/8/96

CC: NDA 20-682 (orig., 1 copy), HFD-510(Rhee, Ysern), HFD-850(Lesko), HFD-870(M. Chen, Fossler, Ahn, Drug File, Chron. File, Reviewer File), HFD-340 (Vish)
9/19/96

SEP 11 1996

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

NDA 20-682 CHEMISTRY REVIEW # 1 DATE REVIEWED: 09-SEP-1996

<u>Submission Type</u>	<u>Document Date</u>	<u>CDER Date</u>	
Original	28-DEC-1995	29-DEC-1995	User fee I.D. N° 2928
Correspondence	18-JUN-1996	19-JUN-1996	
	02-JUL-1996	05-JUL-1996	

NAME & ADDRESS OF APPLICANT: Bayer Corporation Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516-4175
Phone (203) 937-2000 931-5145

DRUG PRODUCT NAME	Proprietary:	GLYSET
	Nonproprietary Established/USAN:	Miglitol Tablets
	Code Name	BAY m 1099
	Chem. Type/ Ther. Class:	1 S

PATENT STATUS: U.S. Patent N° 4,639,436 (drug, drug product, method of use) to Bayer AG.
Exp. 27-JAN-2004

PHARMACOLOGICAL CATEGORY/INDICATION: Inhibitor of α -glucosidase. Hypoglycemic agent.

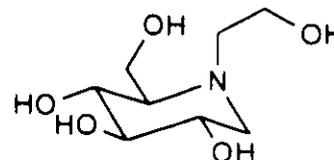
DOSAGE FORM: Tablets

STRENGTHS: 25, 50 and 100 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: R

CHEMICAL NAME/ STRUCTURAL FORMULA:



$C_{11}H_{19}NO_4$
F.W. = 207.2 g/mol
CAS N° 72432-03-2

3,4,5-Piperidinetriol, 1-(2-hydroxyethyl)-2-(hydroxymethyl)-, [2R-(2 α ,3 β ,4 α ,5 β)]

CONCLUSIONS & RECOMMENDATIONS: The application is **approvable** from the Chemistry viewpoint pending a favorable **Environmental Impact Assessment** evaluation and satisfactory response to the deficiencies.

Orig. NDA 20-682
cc: HFD-510/Division File
HFD-510/Fleming/Galliers/Misbin/Moore/JRhec/Ysem
HFD-820/Chiu

R D Init by:

Stephen H. Moore
9/11/96

Xavier Ysem
Xavier Ysem, PhD
filename: 20682_1.nda

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR
GLYSET™
(miglitol)

Oral Tablets 25, 50, and 100-mg

NDA 20-682

Division of Metabolic and Endocrine Drug Products
(HFD-510)

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

GLYSET™

(miglitol)

Oral tablets 25, 50, and 100 mg

NDA 29-682

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

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

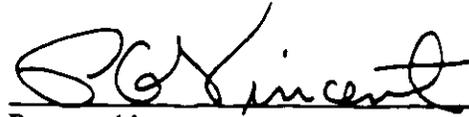
In support of their new drug application for GLYSET™, Bayer Corporation has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) in the Tier 0 format which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Miglitol is a chemically synthesized drug which is administered as 25, 50, and 100 mg oral tablets in the treatment of diabetes mellitus. The drug substance is manufactured by Bayer AG's Wuppertal-Elberfeld facilities in Germany. The finished drug product is manufactured at Bayer Corporation's facilities in Connecticut and will be used throughout the United States.

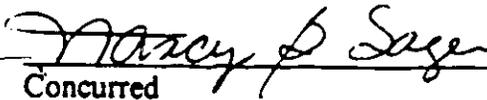
Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed incinerator.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

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

10/30/96
DATE


Prepared by
Phillip G. Vincent, Ph.D
Environmental Scientist
Center for Drug Evaluation and Research

10/30/96
DATE


Concurred
Nancy Sager
Acting Supervisor/Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

OCT 30 1996

SENSITIVE

REVIEW
OF
ENVIRONMENTAL ASSESSMENT

FOR

GLYSET™

(miglitol)

Oral Tablets 25, 50, and 100 mg

NDA 20-682

DIVISION OF METABOLIC AND ENDOCRINE DRUG
PRODUCTS
(HFD-510)

CENTER FOR DRUG EVALUATION AND RESEARCH

DATE COMPLETED: 10/23/96

SUMMARY

A FONSI is recommended.

The EA for GLYSET™ (miglitol) tablets (25, 50, and 100 mg) has not been resubmitted revised EA under the Tier 0 format. The firm, Bayer Corporation, has provided a response to the EA review #1 only. The EIC calculation to establish the 1 ppb Tier 0 limit shows that the EIC = 0.53 ppb, therefore a Tier 0 format EA is adequate.

ENVIRONMENTAL ASSESSMENT

GLYSET™

(miglitol)

Oral Tablets 25, 50, and 100 mg

NDA 20-682

1. Date:

EA Dated: November 20, 1995

EA Date Signed: November 20, 1995

This is obviously as post dated signature.

CSO: Mike Johnston/HFD-510

EA Review #1 Started: 07/29/96

EA Review #1 Draft Completed: 07/31/96

EA Review #1 Completed: 08/28/96

EA Review #2 Completed: 10/23/96

2. Name of applicant/petitioner:

Bayer Corporation
Pharmaceutical Division

3. Address:

400 Morgan Lane
West Haven, CT 06516

END

BT
