

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-357/S019

MEDICAL REVIEW(S)

NDA 20357 Glucophage in Pediatric Patients

Introduction	3
Regulatory Documents	3
Review of pediatric exclusivity protocols	5
Comments on Study 038 : PK study	7
Study 039: double-blind comparison Metformin vs placebo	8

**APPEARS THIS WAY
ON ORIGINAL**

Introduction:

The purpose of this submission is to revise the Glucophage label for use in children. Two studies were submitted, a PK study in children taking insulin and a double-blind placebo controlled trial in pediatric patients not taking any antidiabetic medications. The protocols were developed in consultation with the Division and were the basis of the written request from ODE 2 from which pediatric exclusivity was granted. For the sake of maintaining historical continuity, I have reproduced my initial review of the IND protocols. This appears ahead of my review of the completed studies as submitted in the NDA.

Regulatory documents:

Initial Written request	Dec 23, 1998
Revised WR	May 12, 1999
sNDA submitted	February 15, 2000
supplement	February 24, 2000
supplemental Information	August 9, 2000

Debarment and financial disclose

The Sponsor, Bristol-Myers Squibb (BMS), submitted debarment and financial disclosure documents on February 15, 2000. I have examined these documents and found them to be acceptable:

The following financial disclosure information has been submitted:

- 1 Form OMB No. 0910-0396. The applicant certifies that BMS has not entered into any financial arrangement with the clinical investigators named in the lists included in the NDA whereby the value of compensation to the investigator could be affected by the outcome of the study.
- 2 The applicant further certifies that none of the listed clinical investigators disclosed a proprietary interest in the product or an equity interest in BMS.
- 3 The applicant certifies that no listed investigator was the recipient of other payments such as honoraria, consultation fees, research grants, or compensation in the form of equipment from BMS.
- 4 List of investigators from whom completed financial disclosure forms were received.
- 5 Certification pursuant to 21 CFR 54.5(c) that the applicant acted with due diligence to obtain financial disclosure information from a list of investigators from whom completed forms were never received.
- 6 List of investigators not submitting financial disclosure information and the studies to which they contributed data.
- 7 The investigators listed as not submitting financial disclosure forms each contributed data from single sites in large, multicenter trials. Analyses of efficacy data in this NDA did not reveal any significant effect of center on outcomes. Furthermore, the

data on both safety and effectiveness were consistent across the multiple trials submitted to the NDA. In sum, the absence of financial disclosure information from the investigators listed does not call into question the overall integrity of the data submitted.

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ON ORIGINAL**

-Review of Pediatric Exclusivity protocols - (original text given in italics from review of May 28, 1999)

IND _____

Metformin - Glucophage

Medical Officer's Review - submission of September 18, 1998 and subsequent revisions

Pediatric Exclusivity Protocols:

There was much discussion between the Sponsor, Bristol-Myers Squibb and the Division about what would constitute an appropriate pediatric study. BMS originally proposed a double blind placebo-controlled study of patients who were already taking glucophage. The Division felt that recruitment of patients who were already on Glucophage would not constitute a representative sample of children with type 2 diabetes. In addition we felt that it would be contrary to congressional intent for children to be taken OFF their medication for the purposes of doing a trial to gain marketing exclusivity. Finally, agreement was reached that requirements for pediatric exclusivity would be met by a double-blind placebo-controlled study of metformin monotherapy (protocol 039) and the pharmacokinetic data generated in protocol 038. Protocol 038 is already on going, but only the PK portion is to be part of the exclusivity request.

Protocol 039 (March 23, 1999)

Purpose : Evaluate efficacy of metformin vs placebo in adolescents with type 2 diabetes in a 16 week study using change in fasting plasma glucose as the primary variable. Secondary variables are changes in HbA1c, body weight and serum lipids.

Design: Double-blind placebo controlled parallel study for 16 weeks followed by open-label extension to demonstrate durability of response and to assess safety. The initial dose of metformin of 500-mg bid is increased to 1000 bid as tolerated. Rescue criteria based on capillary glucose levels are 230 mg/dl at 2 weeks, 180 mg/dl at 4 weeks and 140 mg/dl at 6 weeks and beyond. Rescue treatment for patients on placebo will be metformin. Rescue treatment for patients on metformin will be insulin. Patients who receive rescue treatment will be followed for the full 52 weeks to assess safety. An interim analysis will be performed when 36 patient have completed 8 weeks of double blind treatment. A DSMB can recommend that accrual to the blinded comparison be stopped if there is fall in FPG with p value <0.025. In case this recommendation is made, patients will be treated with metformin open label to complete the 52-week safety evaluation.

Study population: 72 patients with type 2 diabetes ages 8-16, but FPG < 240 mg/dl. BMI will be > 50% for age. C peptide must be > 1.5 ng/dl 90 minutes after a Sustacal challenge. Patients cannot be included if they have taken metformin within 3 months or troglitazone within 6 months. Patients on sulfonylureas can be included if their HbA1c exceeds 7.5% and have gained weight while on SFU therapy. SFU is discontinued 28 days prior to randomization. Patients with markers of type 1 diabetes are excluded, as are patients with a serum creatinine > 1.0 mg/dl or abnormal creatinine clearance.

Protocol 038 (as revised October 22, 1998)

Purpose: To gain experience with the use of metformin plus insulin vs insulin monotherapy in adolescents with type 2 diabetes and to elucidate the pharmacokinetic profile for metformin in these patients.

Design: Open label study in adolescent patients with type 2 diabetes who are being treated with insulin. Subjects will receive metformin 500-1000 mg bid with insulin or insulin alone according to a 2:1 randomization. The starting dose is 500 mg before breakfast and dinner. The dose can be increased to 1000 mg before breakfast and dinner after one week based on tolerability. Patients must be on insulin already at the time of screening or inadequately controlled on oral agents (see below). Insulin therapy is continued after screening but oral agents are discontinued 28 days before randomization. Patients coming off oral agents, treatment with insulin is started at least 14 days before randomization. The starting dose of insulin is at the discretion of the investigator. The insulin dose is titrated according to a schedule given in the protocol. Efficacy measures are changes in HbA1c FPG, insulin dosage, weight and serum lipids at 16 and 52 weeks. PK variables (C max, T max, AUC, t 1/2, and % UR) will be assessed in 24 subjects after 1 week of 500 mg bid. The metformin is given as 500 mg tablets with breakfast and dinner. For the PK study a pre-dose sample is taken at 7:30 am. Patients are then fed breakfast. Post-dose samples are taken at 1,2,4,6,8 and 11 hours after the 500-mg dose. The second metformin tablet is given before dinner at 6:30 pm after drawing the 11-hour sample.

Study population: 100 adolescents ages 8-16 (age limit lowered from 10 to 8 on June 1 1999) with type 2 diabetes. Patients must have FPG > 180 mg/dl and HbA1c >7% at screening AND be on oral hypoglycemic therapy (except troglitazone) OR be on insulin already at the time of screening. Other exclusion criteria are the same as described for protocol 039.

Robert I Misbin MD.

Medical Officer

HFD 510: IND — NDA20357/misbin/malozowski

May 28, 1999

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ON ORIGINAL

Study 038 – PK study

To satisfy the requirements for pediatric exclusivity, the Sponsor performed a PK study in pediatric patients on insulin who had been on metformin for at least one week. Of the total of 32 patients, 5 had to be excluded because of a missed dose or because the plasma metformin levels were too low. Mean data from the 26 remaining patients showed much lower C max and AUC measurements than with adult patients. The PK reviewer concluded that a problem with compliance was the most likely explanation for the discrepancy. This also appears to be the most likely explanation to me. Although a small (statistically insignificant) decrease in t1/2 could potentially be explained by good renal function in these young patients, but the low AUC and C1/2 are enigmatic. There is no reason to explain why children should malabsorb metformin. Also, these variables did not appear to be related to the age of the pediatric patients. If the findings were real, one would expect that 16 year olds would be closer to adults than 12 year olds. But this was not the case. The PK reviewer has recommended that the PK study be repeated with adults and children in the same study and with drug given under observation.

Subject group	AUC (ug.hr/ml)	C max(ug/ml)	T1/2
Pediatric subjects	4.49	0.73	3.7 hrs
Adults	8.30	1.22	4.1 hrs

In this study, one patient had a suicide attempt with study medication. (2000 mg/d) during the run-in period. The episode resolved and metformin was withdrawn.

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Study 039

There were 82 patients who entered double-blind treatment, 42 on metformin and 40 on placebo. Their average age was 14 years. Although patients as young as eight were eligible, the youngest patient studied was 10 years old. 18% of patients were between 10-12 years old. Approximately 37% were White, 30% Black and 22% Latino. 30% were male. The average weight was 91.6 kg with average BMI of 34. 83% were at or above the 75 percentile for BMI. There were slightly more White patients in the metformin group than placebo (17 vs 13) and slightly fewer black patients (11 vs 13). The mean BMI were the same in both groups (34.2 vs 33.9).

At the end of double-blind therapy, 83% of metformin patients and 78% of placebo patients were receiving the maximal dose of four tablets.

As shown below four patients on metformin required rescue because of hyperglycemia compared to 26 patients on placebo (p<0.001).

	Metformin	Placebo
Number Enrolled	42	40
Discontinued during double blind period	6 (14%)	4 (10%)
Required "rescue"	4 (9%)	26 (65%)
Unblinded following DSMB recommendation	13(31%)	7 (18)
Completed 16 weeks double-blind therapy	19(45%)	3 (7.5%)

Enrolled patients –

Baseline measures:	Metformin	Placebo
FPG	167	199
HbA1c	8.3	9.0
Stimulated C Peptide ng/ml	7.4	6.5

	Metformin n=37	Placebo n=36	Difference(M-P)
Baseline FPG	163	192	
Last FPG	126	207	
Adjusted mean change	-43	21	-64*

*P<0.001 Based on ANCOVA using baseline as covariant.

Placebo patients had a mean HbA1c of 8.9% at baseline and the mean last HbA1c value was also 8.9%. Metformin patients had a mean baseline of 8.2%, which fell to 7.2% at 16 weeks. The adjusted mean difference was -1.2% ($p < 0.0001$ ANCOVA using baseline as covariant).

No demographic factors appeared to affect efficacy.

From mean baseline values of about 180 mg/dl, there was a mean placebo-subtracted fall in total cholesterol of 10.4 mg/dl ($p = 0.043$) and fall in LDL-C of 8.1 mg/dl ($p = 0.053$). The differences between metformin and placebo in changes in HDL and triglyceride were not significant. There were no statistically significant changes from baseline in any group except for the reduction of total cholesterol of 9.7 mg/dl (95% CF 2.7-16.6) in the metformin group. Mean body weight fell 1.5 kg in metformin patients and 0.9 kg in placebo patients ($p = 0.38$). Both groups grew an average of 0.2 cm.

There were no deaths. 43% of patients on metformin and 30% of patients reported gastrointestinal events on placebo. Major AE's were reported in 2 metformin patients (abdominal pain, and seropositive hepatitis B) and 3 placebo patients (poor glycemic control including one report of ketoacidosis). There was one report of asymptomatic hypoglycemic with a glucose value of 39 mg/dl in one metformin patient.

A fall in granulocyte count from 3,560 to 400 after 14 days of metformin was reported in a patient who was withdrawn because of non-compliance (about 13% compliance) with study medication.

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ON ORIGINAL

Open-Label extension

The open-label extension was ongoing when the NDA was submitted. The protocol calls for following each patient up to a total of 52 weeks from randomization. A total of 68 patients (of 73 in the ITT population) entered the open label. They entered under one of the following four scenarios: 16 patients completed the 16 week double-blind therapy; 30 subjects required "rescue" therapy during the double-blind period; 20 subjects were switched to metformin on the recommendation of the DSMB based on the results of the interim analysis; 2 patients on placebo completed the double-blind period but later required rescue therapy and were entered in the open-label extension. The 68 patients are divided into two groups for purposes of presentation of data. 33 patients were enrolled into the open label extension after having been randomized initially to receive metformin during the double-blind period. 35 patients were enrolled after having been randomized initially to receive placebo during the double-blind period. These patients were enrolled into open-label treatment with metformin because they required "rescue", or following the recommendation of the DSMB. Exposure to metformin is given in Table 2A, Table 2B, and Table 2C. In summary, 31 patients initially assigned to metformin and 11 patients initially assigned to placebo were exposed to metformin over 252 days. The final dose of metformin in the patients initially randomized to metformin was 1000 mg in one patient and 2000 mg in 32 patients.

The patients were 75% female with a median age of 14. Twelve patients were between 10-12 years of age. They were 38% White, 29% Black, 21% Latino, and 6% Asian. There were no native Americans. Mean BMI was 32, with 79% at or above the 75th percentile.

One patient discontinued because the protocol violation of exceeding the dose of 2000 mg/d. One discontinued because of non-compliance and two discontinued because of hyperglycemia. Thus, a total of 4/68 patients discontinued

Efficacy:

At the end of the double blind period, patients were allowed to enter open-label extension where they received treatment with metformin. For patients, who received metformin during the 16-week double blind period, this extension trial assessed the durability of efficacy. For patients who received placebo during the double blind period, this extension trial assessed their initial response to metformin. Analysis of the response to metformin in these patients is descriptive. Being open-labeled and uncontrolled, a rigorous statistical analysis of this trial is not possible.

For the patients initially on placebo, this treatment with metformin represented "escape therapy". The duration of double blind placebo treatment was variable and depended on the amount of time it took for the degree of hyperglycemia to satisfy the escape criteria. The tables of data have the following format. The baseline values are given followed by the last double blind values (16 weeks for patients on metformin and a variable amount of time for patients on placebo). Values for the open label extension, to a maximum of 32

weeks, are given next. The first three tables are summaries of the more extensive tables submitted in the NDA and reproduced at the end of this section.

	Mean FPG	
	Metformin N=33	Placebo N=35
Baseline	163	196
Last double blind Mean change (SE)	124 -39 (6)	206 +17 (13)
Open Label		
week 8 Mean change (SE)	139 (n=24) -27 (11)	182 (n=29) -19 (24)
week 16	146 (n=27) -19 (7)	168 (n=24) -25 (14)
week 24	148 (n=29) -19 (9)	164 (n=25) -16 (14)
week 32	157 (n=19) -6 (14)	170 (n=25) -15 (16)

from S.4.1

As shown in the table above, mean FPG fell 39 mg/dl during the 16-week double blind period in patients on metformin and rose 17 mg/dl in patients on placebo. At the initiation of open-label treatment with metformin the mean FPG in the placebo group was 206 mg/dl. This fell to a mean of 168 mg/dl at the end of 16 weeks. This mean decrease after 16 weeks is similar to the mean decrease of 39 mg/dl during 16 weeks of double blind treatment in patients randomized to metformin. That the response to metformin is so similar in both groups should relieve any doubt that the baseline imbalance in degree of hyperglycemia could have led to spurious results during the double blind period. For patients who received metformin during the double-blind period, there is a gradual return of FPG toward baseline during open-label treatment. Similar results were obtained with HbA1c as shown in the table below.

In summary, the initial response to therapy is similar in both groups and there is a return toward baseline during extended open-label treatment in patients who received metformin during the double-blind period.

Mean HbA1c

	Metformin	Placebo
Baseline	8.1 (n=33)	8.8 (n=35)
Last double blind	7.1 (n=33)	8.8 (n=34)
Open label		
Week 8	7.7 (n=28)	8.6 (n=29)
Week 16	7.8 (n=27)	8.0 (n=24)
Week 24	7.9 (n=31)	8.1 (n=26)
Week 32	7.9 (N=18)	7.9 (N=25)

From table S
4.2

Changes in body weight and BMI are shown below. During double-blind treatment mean weight loss in patients on metformin was 1.6 kg and was 0.7 kg in patients on placebo. That patients on placebo lost weight is important, and shows that the rise in FPG in these patients was not simply due to relaxation of dietary management. Placebo patients lost additional weight during open-label treatment with metformin. Patients on metformin during the double blind period showed a mean weight gain during the open label extension. Changes in BMI mirrored changes in body weight.

	Mean Weight		Mean BMI	
	Metformin	Placebo	Metformin	Placebo
Baseline	92.2	81.9	33.9	31.0
Last double blind	90.6	81.2	33.4	30.6
Last open label	91.6	79.8	33.5	29.9

From table S.4.3b

The lack of durability of the efficacy of metformin during the open-label extension presents a problem. We know from the UKPDS trial that escape from monotherapy is part of the natural history of type 2 diabetes. With respect to the children and adolescents

in this trial however, I suspect that decreased compliance is probably a more important factor (see results of PK study).

Safety:

There were no deaths. There were two serious adverse events, but neither was thought to be related to metformin. One patient had exacerbation of preexisting bipolar disease. A second patient took an overdose of a concomitant medication. Two patients experience mildly elevated ALT levels on metformin (74 and 42 IU/L) but have been continued on study medication. Both were considered manifestation of flu-like illnesses which have resolved. Of the total 68 patients, 22 reported gastrointestinal events, 21 had upper respiratory infections, and 19 had headaches.

**APPEARS THIS WAY
ON ORIGINAL**

Labeling issues:

Otherwise

the label is acceptable.

Phase 4

The PK data presented earlier suggests that pediatric patients may be underdosed according to the current label recommendations for adults. One likely explanation is that the pediatric patients were not fully compliant. The PK study needs to be repeated as requested by the PK reviewer. However, even if no PK differences are found under conditions of observed dosing, the problem of poor compliance among pediatric patients would remain. I suspect this is the reason why the glucose reductions seen in the pediatric subjects reviewed here is somewhat less than seen in adults, and why the effect seems to wane after 16 weeks. I believe we should require a phase 4 study to investigate this issue.

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Recommendation:

Pending agreement to a phase 4 study outlined above, the application should be approved.

Robert I Misbin MD
Draft Nov 22, 2000
Final December 5, 2000

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ON ORIGINAL**

/s/

Robert Misbin
12/6/00 02:18:50 PM
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Medical-Officer's Review
NDA 20-357/S019
Glucophage Pediatrics
Submission September 1, 2000 – Safety Update

The submission of September 1, 2000 contained a safety update for this sNDA. My review of December 6, 2000 already contains my comments on the data in this submission, but I inadvertently neglected to include this September 1 submission in the list on page 3 of documents that I had reviewed. This note is to correct that omission.

/s/

Robert I Misbin MD
December 15, 2000

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