CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-202

MEDICAL REVIEW(S)

AUG 29 2000

MEDICAL OFFICER REVIEW

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

APPLICATION #:	**21202**	**APPLICATION TYPE:**	**Commercial NDA**
SPONSOR:	**Bristol Myers Squibb**	**PROPRIETARY NAME:**	**Glucophage XR**
CATEGORY OF DRUG:	**Antidiabetic**	**USAN / Established Name:**	**Metformin XR**
		ROUTE:	**Oral**
MEDICAL REVIEWER:	**R Misbin**	**REVIEW DATE:**	**August 25, 2000**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
11/12/1999	11/12/1999	Commercial NDA	

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:

Overview of Application/Review:

Two randomized placebo-controlled studies of Glucophage XR

One randomized study comparing Glucophage XR to marketed Glucophage

Outstanding Issues:

Recommended Regulatory Action:

New Clinical Studies: _____ **Clinical Hold** _____ **Study May Proceed**

NDAs: Approvable

Efficacy / Label Supp.: ✓ **Approvable** _____ **Not Approvable**

Signed: Medical Reviewer: 1st **Date:** Aug 29 2000

Medical Team Leader: /S/ Date: 5/29/00

21202 - Glucophage XR

Sponsor: Bristol-Myers Squibb
Submitted November 12, 1999

Robert I Misbin MD

August 17, 2000 (draft)
August 24, 2000 (revised)

Introduction

Metformin XR is a slow release formulation of metformin, which has been developed to be taken once daily. The only currently marketed formulation of metformin is Glucophage, which is labeled to be taken twice daily or thrice daily.
The basis of approval of Metformin XR to treat type 2 diabetes is two placebo-controlled trials and one active controlled trial using Glucophage is the comparator. All three trials used one dosage form of 500 mg.

PK data are reviewed by Robert Shore. An important finding is a small lack of dose proportionality when more than one 500 mg Metformin XR tablets are taken together. This is summarized below:

Treatment	C max (ng/ml)	AUC (ng.hr/ml)
500 mg	789	8828
1000 mg	1261	14488
2000 mg	2251	26667

APPEARS THIS WAY
ON ORIGINAL

Regulatory statements regarding documents reviewed

NDA 21-202 submitted November 12, 1999
Safety update submitted March 10, 2000
Case report of death and lactic acidosis submitted July 11, 2000

Debarment and financial disclose
The Sponsor, Bristol-Myers Squibb (BMS), submitted debarment and financial disclosure documents on November 12, 1999. 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.

Inspections: DSI inspected three sites. The inspections were "unremarkable". This information is contained in a report from Roy Blay of DSI dated June 7, 2000

Placebo-controlled studies

138-010

This was a 24 week placebo controlled trial in patients with type 2 diabetes whose hyperglycemia was inadequately controlled (HbA1c 7-10%) by diet and exercise alone. Following a two week single-blind placebo run-in patients were randomized (2:1) to Met XR or placebo. 240 patients were assigned randomized therapy. Treatment was initiated at 500 mg once daily and increased to 500-mg twice daily after one week. After 12 weeks of therapy, patients whose HbA1c was 8% or above were withdrawn from the trial. The dose was increased to 500 mg tid in patients whose HbA1c was 7-8%. For patients whose HbA1c was < 7% the dose was kept constant at 500 mg bid. Double blind treatment continued for an additional 12 weeks, but the primary measure of efficacy was reduction of HbA1c at 12 weeks.

87% of the patients were white, 60% were male. Mean baseline HbA1c was about 8%. In placebo patients there was a mean rise in HbA1c of 0.12 and 0.21 at 12 and 24 weeks respectively compared to mean reductions of 0.57 and 0.62 in patients on metformin XR. ANCOVA adjustment for baseline is shown in the table below. The placebo-subtracted reduction of HbA1c was 0.65 and 0.79 at 12 and 24 weeks respectively. Both finding were highly significant ($p<0.001$).

Change in HbA1c at 12 and 24 weeks (or last available measurement)

	12 weeks		24 weeks	
HbA1c	Placebo n=79	Met XR n=155	Placebo n=79	Met XR n=156
Baseline	7.88	8.04	7.88	8.04
Week 12/24	8.00	7.47	8.09	7.42
Adj Mean chng	+0.09	-0.56	+0.19	-0.62
Diff		-0.65		-0.79

From table 11.1.1.4.1

The placebo-subtracted reductions in FPG and fructosamine were also highly significant, but there were no significant changes in serum lipids or insulin levels.
Mean baseline fructosamine was about 333 umol/L. In placebo patients it rose 4.5 and 6.5 at 12 and 24 weeks respectively. On Met XR 1000 mg qd it fell 31 and 34 umol/L at 12 and 24 weeks, respectively. The placebo-subtracted change was -35.7 and -40.5 at 12 and 24 weeks, both highly significant $p<0.001$. Mean baseline FPG was about 175 mg/dl. There was little change in placebo patients. In patients on metformin, the

placebo-subtracted reduction in FPG was 21 and 25 mg/dl at 12 and 24 weeks respectively.

Mean body weight fell by 0.2 kg in Met XR patients and 1.0 kg in placebo patients. The difference of 0.9 kg was significant (p=0.012) in favor of more weight reduction on placebo. This result is different from other studies.

Safety

There were no deaths. Nausea and/vomiting was reported in 9% of patients on metformin XR and 4% of patients on placebo. There was one hospitalization for recurrent vomiting in a patient taking metformin XR. Discontinuation because of an adverse event occurred in 4.4% of patients on metformin compared to 2.5% on placebo.

Study 138-036

This was a 16 week placebo controlled double blind dose-response study in patients whose hyperglycemia was inadequately controlled (Hba1c 7-11 at screening) on diet and exercise alone. Following a two week placebo run-in, patients were randomized to the placebo or following doses of metformin XR: 500mg qd, 1000mg qd, 1500mg qd, 2000 mg qd or 1000mg bid. Patient randomization was 111-125 in each arm. 84% of patients were white and 52% were male. The mean age was about 55 years.The mean BMI in each treatment group ranged from 29.7-30.9

The primary measure of efficacy was change in HbA1c at 16 weeks. As shown in the table below, there was a small rise in HbA1c in placebo patients and a fall in metformin patients. All metformin groups were different from placebo ($p<0.0001$). A dose-response relationship was seen up to 1500 mg given once per day. 2000 mg once per day was the same as 1500 mg once per day. However, 1000-mg bid appeared to give somewhat better results although the difference was probably not statistically significant. The withdrawal rate due to inadequate glycemic control was 16.2% among placebo patients, 6% in all metformin XR once daily groups, and 3.3% in the twice-daily arm.

Change in Hemoglobin A1c (HbA1c)

		METFORMIN-XR				
HbA1c	Placebo	500 qd	1000 mg	1500 qd	2000 qd	1000 bid
Baseline	8.36	8.20	8.40	8.33	8.38	8.43
16 weeks	8.47	7.81	7.78	7.47	7.54	7.34
Mean chg	0.11	-0.39	-0.61	-0.86	-0.84	-1.10
Adj chg	0.11	-0.44	-0.60	-0.87	-0.83	-1.06
Difference	-----	-0.55	-0.71	-0.98	-0.95	-1.17

Change in secondary measures of efficacy

Fructosmn	Placebo	500	1000	1500	2000	1000 bid
Baseline	337	339	347	344	340	342
Adj chg	4	-20	-31	-35	-38	-48
Difference		-24	-35	-40	-42	-53
FPG	180	183	184	179	181	182
Adj chg	8	-15	-19	-29	-30	-34
Difference		-23	-27	-36	-37	-41

A placebo-subtracted reduction in total cholesterol of 8.3 mg/dl ($p=0.020$) and 10.2 ($p=0,005$) was seen in with 2000 mg qd and 1000 mg bid respectively. Statistically significant reductions vs placebo in LDL cholesterol was observed in all metformin

groups. The largest reduction was 12.1 mg ($p<0.001$) in the 1000 mg-bid group. There were no consistent changes in HDL, triglyceride or body weight.

Safety:

One patient on 1500 mg Met XR experienced sudden death. Gastrointestinal complaints were the most common AE's. Nausea was reported in 12.9% of patients on metformin compared toll 3.4% of patients on placebo. Dropout rate because of an adverse event was 0.9% for placebo and 3.2%, 2.5%, 4.2% 3% and 0.8% for 500 qd, 1000mg qd, 1500mg qg, 2000mg qd and 1000 mg bid respectively. .

Comment: There appears to be no difference in the efficacy of metformin XR at 1500 or 2000 mg given once daily. Although the comparison would probably fail statistical analysis, it appears that 2000 mg of Metformin XR is better given twice daily than once daily (see table below). This may be due to the lack of dose proportionality noted from the PK data (see p2).

	2000 mg once daily	1000 mg bid
HbA1c, % units	-0.95	-1.17
FPG, mg/dl	-37	-41
Fructosamine, umol/L	-42	-53
Total cholesterol, mg/dl	-8.3	-10.2
Drop-outs: Lack of efficacy	6.0%	3.3%
Adverse event	3%	0.8%

Data are summary from earlier tables, efficacy data are placebo-subtracted. Drop-out data are raw numbers.

Study 138-012 - Active controlled comparison to immediate release metformin (Met IR).

This was a double blind study to compare two doses of metformin XR given once daily to metformin IR 500 mg twice daily in patients who had already been taking metformin IR 500 mg twice daily for at least 8 weeks. Randomization to one of the three-blinded treatments was preceded by a two-week open label run-in of metformin IR 500-mg bid. Inclusion criteria required patients to have HbA1c 8.5% or under and FPG < 200 mg/dl at screening. Initial dosing was 500 mg Met IR bid compared to once daily 1000 mg or 1500 mg Met XR. After 12 week, patients whose HbA1c remained over 8% could be given an additional 500 mg for the following 24 weeks.

There were 217 patients randomized to receive blinded treatment. 75% were white and 57% were female. The female preponderance existed in all three groups. The mean age was 54 years. Mean BMI was 31-33.2 kg/m2. Mean baseline HbA1c was 7.02%. Mean Baseline FPG was 131 mg/dl.

Changes in HbA1 at 12 and 24 weeks are shown in the following tables. Although there were no statistically significant differences among the treatment arms, it worth noting that only patients on metformin XR 1000 mg showed statistically significant rise in HbA1c from baseline.

Change in HbA1c at 12 weeks

	Metformin IR* 500 mg bid n=66	Metformin XR 1000 mg qd n=70	Metformin XR 1500 mg qd n=65
Baseline	7.03	6.98	7.02
Week 12	7.18	7.21	7.06
Mean change	0.15	0.23	0.04
95% CF	-0.02, 0.31	0.10, 0.37	-0.08, 0.15

Change in HbA1c at 24 weeks

	n=63	n=67	n=64
Baseline	7.02	6.97	7.02
Week 24	7.08	7.22	7.16
Mean change	0.06	0.25	0.14
95% CF	-0.08, 0.20	0.09, 0.40	-0.02,0.29

Table 11.2.1.4.1

* Metformin IR 500 mg bid was baseline therapy

Secondary measures of efficacy are shown in the table below. There were small mean increases in all groups in all measures of glycemia The increases were smallest in patients on Met-XR 1500 mg but the differences between treatment groups were not great.

Change from Baseline

FPG mg/dl	Met IR 500 bid	Met XR 1000qd	Met XR 1500 qd
12 weeks	12.9	9.5	3.7
24 weeks	14.0	11.5	7.6
Average PG, mg/dl			
12 weeks	6.09	9.31	2.38
24weeks	8.31	15.67	5.54
Fructosmin umol/L			
12 week	8.9	16.2	4.3
24 weeks	12.8	18.1	9.0

The proportion of patients who failed to achieve HbA1c under 8% is shown in the table below. Given the fact that patients had to have an HbA1c of 8.5% or less to be included in the study, these numbers have little importance.

Failure to achieve reduction in HbA1c to under 8%

HbA1c 8% or more	Met IR 500 bid	Met XR 1000 qd	Met XR 1500qd
12 weeks	20%	20%	12.%
24 weeks	16%	19%	19%

In the preceding tables, it is worth bearing in mind that patients were allowed an up-titration of 500 mg at week 12 for HbA1c of 8% or higher . This dose increase occurred in 11/66(17%) of patients on Met IR, 13/70(19%) of patients on Met XR 1000 mg and 8/65(12%) of patients on Met XR 1500 mg.

Among patients who received the additional 500 mg qd because of HbA1c > 8% at 12 weeks, the proportional who responded was about the same in all three groups: 3/11 on Met IR, 4/13 on Met XR 1000mg and 3/8 on Met XR 1500 mg. The Sponsor appears to attach great significance to the three patients whose HbA1c fell below 8% when their dose of Met XR was increased from 1500 to 2000 mg (see labeling comments).

Lipids and weight:

Serum lipids were little changed. With respect to LDL chol, patients on Met IR 500 mg bid showed a mean fall of 0.3 mg/dl and 3.9 mg/dl at 12 and 24 weeks. Patients on Met XR 1000 mg qd showed decreases of 1.9 and 5.8 mg/dl at 12 and 24 weeks. Patients on Met XR 1500 qd showed a mean rise of 2.5 mg/dl at 12 weeks but a mean fall of 6.3 mg/dl at 24 weeks. Mean triglyceride levels were unchanged for patients on Metformin IR 500-mg bid, but increased in patients on both doses of Metformin XR. For patients on

1000 qd the mean increase was 51 and 34 mg/dl at 12 and 24 weeks. For patients on 1500-mg qd the mean increase was 36 and 42 mg/dl at 12 and 24 weeks. Mean body weight remained unchanged in all groups.

Safety

One patient died during treatment with Met XR 1500 mg. She was a 65-year-old women hospitalized via an emergency room because of chest tightness and dyspnea. She died during that admission with a diagnosis of lactic acidosis and "septic shock due to overwhelming pneumonia". In reviewing her hospital records, I saw no evidence of septic shock. Cultures of blood and sputum were negative and her white count was normal. I believe a more likely cause of the death was acute myocardial infarction with pulmonary edema. Regardless of the exact cause of death, the diagnoses of lactic acidosis rests solely on a bicarbonate of 6 mEq/L that was measured during a fatal cardiac arrest. The only pH value is 7.7, which I presume was measured after sodium bicarbonate had been administered. There are no lactate measurements at all. This case would not have fulfilled the diagnostic criteria for lactic acidosis described by Stacpoole and Misbin (N Engl J Med 1983;309:390-396) and updated by Stacpoole et al (N Engl J Med 1992;327;1564-9).

Withdrawals due to adverse events were due to surgical procedures or acute illnesses. Diarrhea was reported in 22.5% of subjects on Met XR 1500, 8% of patients on 1000 mg compared to 4.2% of patients on Met IR. By contrast, nausea and/or vomiting was reported by 9.9% of patients on Met IR compared to 6.7% and 2.8% of patients on Met XR 1000 mg and 1500 mg respectively.

	Met IR 500 mg bid n=71	Met XR 1000 mg qd n=75	Met XR 1500 mg qd n=71
ADE	18	22	24
SAE	2	3	5
Death	0	0	1
Withdraw due to AE	1	4	1

APPEARS THIS WAY
ON ORIGINAL

Safety Update

The Sponsor submitted a 120-day Safety Update on March 10, 2000. The total data base consists of 768 patients treated with metformin XR during double blind trials of which 664 completed those trials. There are 510 patients in ongoing open-label extensions. Total exposure to Metformin XR is 830 patients of which 423 had been exposed greater than 180 days.

Data in the safety update are inclusive through November 12, 1999 and do not duplicate reports in the original NDA. Among patients in the long-term open label extension, 18.7% reported gastrointestinal events, 18.1% respiratory, and 11.6% muscloskelatal. One patient died due to trauma in a motorcycle accident. One patient was hospitalized because of diarrhea four days after starting the open-label extension study of Met XR 500 mg qd. There were two other surgical hospitalizations that were unrelated to metformin. 15 patients discontinued treatment because of gastrointestinal adverse events, primary nausea and/or diarrhea.

Comment on Lactic Acidosis -

Phenformin was withdrawn in 1977 because of lactic acidosis (Misbin RI. Ann Intern Med 1977;87:591-5). No other biguanide was approved by FDA until metformin in 1995. From its marketing in May 1995 thru June 1996, FDA received 47 cases of confirmed lactic acidosis, in which 20 patients died. Risk factors such as renal disease or congestive heart disease were present in 43. There were only four cases in which risk factors were not present at the time metformin therapy were started. One of these patients developed well-documented sepsis but recovered. (Misbin et al N Eng J Med 1997; 338, 2650). In view of the presence of other risk factors for lactic acidosis in nearly all cases, and the poor correlation between lactic acidosis and metformin blood levels, Dr Peter Stacpoole has recently speculated that metformin may not cause lactic acidosis at all (Metformin and Lactic acidosis - Guilt by association? Diabetes Care 1998;21:1587-1663). This idea is strengthened by the fact that there have not been cases of lactic acidosis reported to FDA from clinical trials in which Glucophage was used. The total clinical trial experience is about 10,000 patients and includes phase 3 placebo-controlled trials as well as trials in which metformin is added to sulfonylureas, glitazones or acarbose. There are the 7000 patients in the ———— being done by BMS, and 1000 patients in the NIH diabetes prevention trial (The same trial that yielded one death following liver transplant in a patient on troglitazone and one additional case of severe hepatitis among the approximately 600 patient treated with troglitazone). The one case of lactic acidosis reported with Metformin XR in this NDA appears to break a perfect record. But even here, the diagnosis of lactic acidosis is based on a low bicarbonate level determined during a fatal arrest.

The major argument against "guilt by association" is the observation that a metformin overdose can cause lactic acidosis. This is true even for intentional overdoses in people who do not have diabetes, but the risk of dying from lactic acidosis due to metformin overdose is low. There was only one fatality among the 13 cases reported by Lelau et al. (Diabetes Care1998; 21: 2036-2037). This is consistent with my earlier observation that other factors, primarily congestive heart failure, seems to account for most of the deaths. in metformin-associated lactic acidosis (Misbin et al N Eng J Med 1997; 338, 2650.) Lactic acidosis occurs in the absence of metformin and has a mortality of over 80%. (Stacpoole and Misbin. N Engl J Med 1983;309:390-396 and Stacpoole et al. N Engl J Med 1992;327;1564-9).

When all the available information is considered, I believe that the risk that taking metformin leads ot lactic acidosis is small. There is no evidence that metformin causes lactic acidosis when it is used as directed. Death in patients with lactic acidosis on metformin is almost always associated with heart failure and/or renal failure. Metformin intoxication does cause lactic acidosis but most of these patients survive. My own belief

is that most of the cases of lactic acidosis in patients on metformin have nothing whatever to do with metformin. The case of "lactic acidosis" in this application is a good example.

Labeling Issues:

The label contains few data from the clinical trials of Metformin — By giving only verbal descriptions the Sponsor appears to want to finesse certain issues that may be of clinical importance.

P2- Why are the no data about HbA1c reduction with Metformin XR. At a minimum the comparison of Metformin XR to Glucophage IR at 24 weeks from study 012 should be included.

P4- The statement that '[redacted] is based on just 3 patients who were given the higher dose after 12 weeks of 1500mg. Given that 12 weeks is insufficient time to see the full effect on HbA1c, the small reduction that occurred with dose titration is not convincing. What would have happened if these 3 patients had been given a 500 mg placebo tablet? Study 036 showed that both 1500 mg and 2000 mg gave them same result.

P4 - The effect on LDL is described as '[redacted]' and [redacted] but the rise in triglyceride is described as '[redacted] The label should be revised to include the data and remove the judgmental language.

[redacted]

[redacted]

Summary and Recommendation:

Metformin XR is safe and effective for the treatment of hyperglycemia in patients with type 2 diabetes. The label should include pertinent comparisons so that physicians and patients can make their own assessment. Assuming these revisions are made to the label. I recommend that the application be approved.

/S/

Robert I Misbin MD
HFD 510
Draft August 18,2000
Revised August 25, 2000

APPEARS THIS WAY
ON ORIGINAL

From MOR Review

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