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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-574

Medical Review(s)

MEDICAL OFFICER REVIEW

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

APPLICATION #: 21574 APPLICATION TYPE: NDA.....
SPONSOR: ANDRX PROPRIETARY NAME: Metformin
CATEGORY OF DRUG: Antidiabetic USAN / Established Name: Fortamet.....
ROUTE: Oral.....
MEDICAL REVIEWER: Robert I Misbin.. REVIEW DATE: Feb 20, 2004.....

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
Dec 19, 2002	Dec 23, 2002		
April 16, 2003	April 17, 2003	Safety update	

Dec 19, 2003	RESPONSE to "APPROVABLE" Letter of October 17, 2003
February 18, 2004	Final label

Metformin XT once daily is nearly as effective in lowering HbA1c levels as Glucophage twice daily. This shortcoming of Metformin XT is potentially offset by the convenience of once a day dosing. The safety profile of Metformin XT and Glucophage are similar. **The submission of Dec 19, 2003 establishes equivalency (2x 500mg=1x1000mg) of the 500 mg and 1000 mg tablets. The final label, dated February 18, 2004 is acceptable.**

The 500 mg and 1000-mg tablets can be approved.

Signed: Medical Reviewer: Robert I Misbin MD Date: Feb 20, 2004

Medical Team Leader: _____ Date: _____

Comments on Sponsor's Response to Approvable Letter: 3
Labeling changes

Original Review:

Executive Summary

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Comments on Sponsor's Response to Approvable Letter

FDA issued an approvable letter on October 17, 2003. The major deficiency was failure to have demonstrated bioequivalence between the 500 mg and 1000 mg tablets. The need for changes in the proposed label was also cited.

In the submission of Dec 19, 2003, the Sponsor submitted new data that establish equivalency (2x 500mg=1x1000mg) of the 500 mg and 1000 mg tablets. Appropriate labeling changes were made but additional changes were still needed. The NDA could be approved assuming the label were revised as described below:

Request for Changes to Label of Dec 19:

Changes should be made to table 4 and accompanying text proposed by Dr Sahlroot. In addition, the following statement under Table 4

should be removed entirely or revised to state:

“Results of this study also indicated that neither Fortamet nor immediate release metformin were associated with weight gain or increase in body mass index”

Tables 5 and 6 and accompanying text should be removed.

Q4 in the PPI should be revised to read:

“Fortamet, as well as other formulations of metformin, lowers the amount of sugar in your blood...etc...”

The following statement under “Recommended Dosing Schedule” should be removed:

[

]

Regulatory statement: The final label, dated February 18, 2004, is acceptable. The NDA can be approved.

Review of Original NDA (review date October 14, 2003)

Executive Summary

I Recommendations:

The efficacy of Metformin XT given once daily is close enough to that of Glucophage twice daily, that the two treatment regimens can probably be used interchangeably in most patients. This shortcoming of Metformin XT is potentially offset by the convenience of once a day dosing. The safety profile of Metformin XT and Glucophage are similar. Because dose equivalency (2x 500mg=1x1000mg) has not been established, only the 1000 mg tablet should be approved at present.

II Summary of Clinical Findings

Metformin XT is a long acting preparation of metformin to be marketed under the trade name, Fortamet. It was designed to be given once daily and achieve the same glucose control as immediate release Metformin given twice daily. The Sponsor performed three phase 3 trials. Two of these were comparisons to immediate release Metformin (Glucophage) and the third was a placebo-controlled study.

Study 301 was designed to demonstrate the non-inferiority of Fortamet given once daily at dinner to Glucophage give twice daily in patient who had been taking Glucophage for at least 12 weeks. As shown in the table, mean HbA1c rose in both groups. Using a non-inferiority margin of 0.4% units for change in HbA1c, Fortamet was non-inferior to Glucophage with respect to maintaining glucose control. The safety/tolerability profile of Fortamet and Glucophage were similar.

Mean HbA1c study 301.

	N (ITT)	Baseline	Endpoint	Change	Difference
Met XT	313	7.02	7.42	0.40	0.27
Glucophage	322	7.08	7.21	0.13	

Study 302 was done to study safety. Its design was similar to study 301 except that there was a forced to titration to 2000 mg or 2500 mg (the maximal labeled dose of metformin). As was the case with trial 301, mean HbA1c levels rose somewhat but the rise was similar on both drugs (see table below).

	Metformin XT			Glucophage		
N=	49	49	49	53	53	53
Mean	7.51	7.70	0.19	7.51	7.85	0.33

The Sponsor was asked to perform an analysis of change in HbA1c in the subset of patients who were naïve to treatment. The purpose of this analysis was to isolate the glucose-lowering affect of study drug from changes in dosing of concomitant antidiabetic medications. As shown in the table below, Metformin XT was about as effective as Glucophage in reducing HbA1c.

HbA1c: Treatment-naïve Patients, ITT

	Metformin XT n=11			Glucophage n=11		
2000mg						
N=	4	4	4	6	6	6
Mean	8.30	7.60	-0.70	7.92	7.40	-0.52
2500mg						
N=	7	7	7	5	5	5
Mean	6.83	6.36	-0.47	7.36	7.28	-0.08
Total						
N=	11	11	11	11	11	11
Mean	7.36	6.81	-0.55	7.66	7.35	-0.32

Study 303 was a four month, double-blind, placebo-controlled trial in patients who were naïve to pharmacologic treatment or had been off antidiabetic medication at least 8 weeks. As shown in the table below, the placebo subtracted LS mean change for HbA1c in the ITT population was -0.78 (p=0.028).

Change in HbA1c baseline to endpoint ITT

Treatment	N	Baseline, mean	Endpoint, mean	Change
Metformin XT	19	8.54	7.28	-1.26
Placebo	33	8.65	8.23	-0.43

The safety/tolerability profile of Metformin XT was similar to what has been found with immediate release metformin.

I Introduction and Background

Metformin (Glucophage) has been available in the USA since 1995 and is generally considered the treatment of choice for obese patients with type 2 diabetes. It can be used as monotherapy or in combination with other antidiabetic agents including insulin.

Metformin (Glucophage) is given twice or three times per day in doses ranging from 500 mg bid to 850 mg tid. Gastrointestinal discomfort occurs early in treatment and is the major limiting factor in dose escalation. Most patients can tolerate or become tolerant to the gastrointestinal AE's of metformin. A regimen of 1000 mg bid is common. Glucophage is marketed as 500 mg, 850 mg and 1000 mg tablets. Generic metformin is also available.

Glucophage XR is a once a day preparation of metformin. It is marketed as 500 mg and 750 mg tablets. The maximum recommended dose of Glucophage XR is 2000 mg once daily with the evening meal.

Metformin XT is a long acting preparation of metformin to be marketed under the trade name, Fortamet. It was designed to be given once daily and achieve the same glucose control as immediate release Metformin given twice daily. The Sponsor performed three phase 3 trials. Two of these were comparisons to immediate release Metformin (Glucophage) and the third was a placebo-controlled study.

II Clinically relevant findings from review from other disciplines

Commenting on the efficacy results (HbA1c reduction) from trial 303, the statistical reviewer, Dr Todd Sahlroot, notes:

“Because the lower bound of the CI for the mean difference excluded zero, XT was also statistically inferior to Glucophage ($p < 0.0001$) in addition to being clinically non-inferior”.

This result arises from the use of a non-inferiority margin of 0.4% for the change in HbA1c.

Dr Sahlroot noted that dropouts due to “lack of efficacy” were 5% of XT patients compared to 2% of Glucophage patients ($p = 0.047$)

Dr Sahlroot also questions the “assay sensitivity” of the trial, noting that mean HbA1c levels rose from baseline to endpoint in both treatment arms.

These issues are dealt with in the “Discussion of efficacy” section of this review.

III Pharmacokinetic and Pharmacodynamics Issues:

There are two major PK issues:

The dosage equivalence between the 500 mg and 1000 mg tablets has not been established for the phase 3 and commercial formulations. Indeed, the dose equivalence study of the pilot lot failed.

The PK/relative bioavailability information in the proposed label was derived from studies using the pilot lot and the pilot lots and phase 3 lots were not bioequivalent.

These problems are discussed in Dr Wei's review. From a clinical perspective, I offer the following comments:

Fortamet given once daily is nearly as effective as Glucophage given twice daily. Both preparations of Metformin (Glucophage and Fortamet) show decreasing absorption with increasing dose. This explains, in my judgment, why 1000 mg of Glucophage given twice daily is somewhat more effective than 2000 mg of Fortamet given once daily.

The efficacy of the 1000 mg dose of Fortamet has been established by the clinical trials. But the efficacy of the 500 mg dose of Fortamet has not established by the clinical trials. The 500 mg tablet was always given along with one or two 1000 mg tablets. Given the size of the trials, and variability of response, one cannot expect to distinguish 1000 mg from 1500 mg or 2000 mg from 2500 mg. The 500 mg tablet was never used alone. Therefore, its efficacy has not been established.

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IV Description of Clinical Sources
(See clinical review)

V Clinical Review Methods:

The review was conducted of the hard copy of the summary of the NDA with reference to other documents that had been submitted electronically. No routine inspections of the sites were performed. Although the consent documents were not reviewed, the trials appears to have been conducted in accordance with acceptable ethical standards. The escape criteria for lack of efficacy are praiseworthy. The financial disclosure documentation appears adequate.

Regulatory statements regarding documents reviewed:

The Sponsor, Andrx Labs submitted debarment and financial disclosure documents. The documents are signed by Nicholas Farina, Vice President of Andrx Labs on 11/20/02. I have examined these documents and found them to be acceptable. The debarment statement indicated that the Andrx Labs did not and will use the services of any individual or organization that had been debarred.

The Sponsor makes reference to FDA form 3455. The following financial disclosure information has been submitted:

- 1 Form OMB No. 0910-0396. The applicant certifies that Andrx Labs 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 Andrx Labs
- 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 Andrx Labs.
- 4 List of investigators from whom completed financial disclosure forms were received.

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VI Review of Efficacy

Study 301

This was a double-blind study to evaluate Metformin XT once daily vs Glucophage twice daily in patients with type 2 diabetes who had previously been taking Metformin. A double-dummy design was used to maintain the blind so that each patient received both active drug and placebo for the alternative medication. Metformin XT (or placebo) was given once daily at about 6:00 PM before dinner. Glucophage (or placebo) was given at about 8:00 am before breakfast and 6:00 pm. Eligible patients were to have been on a stable dose of Metformin for at least 12 weeks. For the first 6 weeks, the dose of study medication was titrated to achieve a FPG of 140 mg/dl. For the last 20 weeks the dose was kept constant. Other antidiabetic medications could be continued during the trial at their pre-trial dose.

Inclusion criteria: Patients had type 2 diabetes, 30-70 years of age on a fixed dose of Glucophage 850 to 2550 mg/d for at least 12 weeks. At visit 1 (screening), HbA1c was 9% or less, FPG < 230 mg/dl. Difference in FPG between visits 1 and 2 could not exceed 20% of the higher value. In addition to the standard exclusion criteria, patients could not be using a glitazone in combination with metformin.

Dosing: Randomization and dosing began at visit 3 (2 weeks after screening). Dosing was initiated based on the previous dose of metformin and the FPG. The dose was titrated in an attempt to achieve a FPG of 140 mg/dl. The minimal dose was 1000 mg/d and the maximal dose was 2500. Study medications were administered as 500 mg or 1000 mg tablets or matching placebos. Doses of 1000 mg and 2000 mg were given as 1x or 2x 1000 mg tablets. The dose of 1500 mg or 2500 mg were achieved by adding a single 500 mg tablet. No change in study medication dose was allowed beyond week 6.

Hypothesis and level of significance: The study was designed to support approval for Metformin XT with the same indications as Glucophage. Metformin XT was required to pass a non-inferiority test vs Glucophage using HbA1c, with a non-inferiority margin of 0.4 and 80% power.

Disposition:

680 patients were randomized. 263/339 (77.6%) of patients randomized to Metformin XT completed the trial compared to 292/341 (84.2%) of patients randomized to Glucophage. 18/339 (5.3%) of patients randomized to Metformin XT withdrew because of **“lack of efficacy”** compared to 8/341 (2.3%) of patients randomized to Glucophage.

Demography:

Patients were 59% male, 75% white, 14% Hispanic and 9% black. The mean age was about 57 years. The mean weight was about 95kg, mean BMI 31.4 The distribution of metformin dose at randomization was < 1500 mg (33%), 1500-<2000mg (19%), 2000 mg or more (48%). Approximately 50% of patients were using insulin secretagogues (mainly Glyburide and Glipizide). Approximately 7% were using insulin. Approximately 40% were using lipid-lowering drugs or ACE inhibitors. About 16 % were using beta blockers. The two arms appeared to be well matched with respect to demographic characteristics.

The dose of study medication at the end of the titration period is in the following table:
% of all randomized patients

Final dose	Metformin XT	Glucophage
1000mg	12.7	10.3
1500mg	8.0	12.9
2000mg	23.6	19.1
2500mg	55.8	57.8

The average final dose was 2119 for Met XT and 2126 for Glucophage. The mean change from baseline was 443 for Metformin XT and 467 for Glucophage.

Result:

	N (ITT)	Baseline	Mean HbA1c Endpoint	Change	Difference
Met XT	313	7.02	7.42	0.40	0.27
Glucophage	322	7.08	7.21	0.13	

From the table shown above, it appears that Met XT and Glucophage were approximate the same in maintaining HbA1c levels. Values rose slightly in both groups. Based on a non-inferiority margin of 0.4%, Met XT passed a test of non-inferiority but only barely. The upper limit of the 97.5% CI for the difference in HbA1c at endpoint is 0.385.

The change in HbA1c based on baseline dose is displayed in the following table. Not unexpectedly, patients taking larger doses of drug at baseline had higher HbA1c levels and the increase at endpoint tended to be greater as well. One notes however, that the rise in HbA1c in patients on Glucophage did not occur in patients taking less than 2000mg per day. By contrast, the rise in HbA1c occurred at all dose levels for patients taking Metformin XT, although it was greatest at the highest dose level.

	Metformin XT			Glucophage		
1000	6.85	7.14	0.29	6.95	6.97	0.02
1500	6.81	7.07	0.26	7.09	7.03	-0.06
2000	7.12	7.57	0.45	7.08	7.25	0.17
2500	7.39	8.09	0.70	7.47	7.93	0.46

As shown in the table that follows the result using the per protocol population was largely the same as with the ITT population. For the per protocol population, the upper limit of the 97.5% CI for the difference in HbA1c at endpoint is 0.300

	N(per protocol)	Mean HbA1c			
		Baseline	Endpoint	Change	Difference
Met XT	255	6.97	7.29	0.32	0.18
Glucophage	287	7.05	7.18	0.13	

In the ITT population, the mean FPG at baseline was about 146 mg/dl in both groups. It rose at endpoint by 10.0 mg/dl with Metformin XT and 4.2 mg/dl with Glucophage. The difference of the LS mean increase was 6.43 mg/dl (95% CI 0.6-12.2). The p value for this difference is 0.03

In the ITT population, the mean fructosamine at baseline was about 290 umol/L in both groups. It rose at endpoint by 16.9 with Metformin XT and 2.3 with Glucophage. The difference of the LS mean increase was 15.5 (95% CI 9.6-21.4). The p value for this difference is 0.0001

Mean fasting plasma insulin levels were about 17.5 uU/ml at baseline and fell about 3.5 uU/ml in both groups. In the PP population, the mean FPG at baseline was about 145 mg/dl in both groups. It rose at endpoint by 6.0 mg/dl with Metformin XT and 2.9 mg/dl with Glucophage. The difference of the LS mean increase was 3.04 mg/dl (95% CI – 2.7, 8.8).

In the PP population, the mean fructosamine at baseline was about 289 umol/L in both groups. It rose at endpoint by 11.6 with Metformin XT and 2.1 with Glucophage. The difference of the LS mean increase was 15.5 (95% CI 3.8, 15.7).

Mean body weight at baseline was about 94 kg. The change was +0.3 kg (95% CI 0.0, 0.6) for Metformin XT and 0.0 kg for Glucophage. BMI was about 31.2. The change was +0.1(95% CI 0.0, 0.2) for Metformin XT and 0.0 for Glucophage.

Lipid levels changed little during the trial. The only value possibly worth noting is a rise in triglyceride from 199 to 246 in patients on Metformin XT. In patients on Glucophage, mean triglyceride levels remained unchanged at 200 mg/dl.

Study 302 – To compare the tolerability and safety of 2000 mg and 2500 mg Metformin XT given once daily to the same dose of Glucophage given twice daily.

This was a double-blind study to evaluate Metformin XT once daily vs Glucophage twice daily when given in doses of 2000 mg or 2500 mg per day. A double-dummy design was used to maintain the blind so that each patients received both active drug and placebo for the alternative medication. Metformin XT (or placebo) was given once daily at about 6:00 pm before dinner. Glucophage (or placebo) was given at about 8:00 am before breakfast and 6:00 pm. “Patients were assigned to either 2000mg or 2500mg as needed in order to achieve at least 100 in each of these high dose groups between the two protocols (301 and 302)”. 56 patients were randomized to Metformin XT and 59 were randomized to Glucophage.

Patients on 1000 mg or less of metformin received 1000 mg initially which was increased to the assigned 2000 or 2500 mg at the rate of 500 mg per week. Patients on 2000 mg or more received their assigned dose of 2000 mg or 2500 mg initially and throughout. Patients on between 1000-2000 mg received 1500-2000mg initially which was increased to the assigned 2000 or 2500 mg. During the first 4 weeks, the dose of any concomitant antidiabetic medication was adjusted at the discretion of the investigator in order to allow for the “protocol-driven” increases to the assigned dose of either 2000 or 2500mg.

Inclusion criteria: Patients had type 2 diabetes, 30-70 years of age HbA1c was 9% or less, FPG < 230 mg/dl.

Statistics: The study was designed to compare the safety of high dose Metformin XT with the same dose as Glucophage. There was no power calculation

Demography:

Patients were about 67% male, 63% white, 23% Hispanic and 13% black. The mean age was about 55 years. The mean weight was about 93kg, mean BMI 31. 68% of patients on Metformin XT and 78% on Glucophage were using insulin secretagogues (mainly Glyburide and Glipizide). Approximate 15% were using insulin. 14/56 patients randomized to Metformin XT and 11/59 patients randomized to Glucophage were receiving no antidiabetic medications. 78% of patients randomized to Metformin XT and 70% of patients randomized to Glucophage had no change in their concomitant antidiabetic medications during the trial (this includes the patients who were taking no antidiabetic medications other than study drugs). Of the patients who did have changes in their other medications, there appeared to be no difference between the two arms with respect to adding new medications, dropping old ones, or changes in dose.

Results:

As shown in the table below, HbA1c values tended to rise over the study but there was no difference between Metformin XT and Glucophage. This result was mirrored in change in FPG, which rose 14 mg/dl in both groups, 152 mg/dl to 166 mg/dl for Metformin XT (p=0.02), and 150 to 164 (p=0.02) for Glucophage.

	Metformin XT			Glucophage		
2000mg						
N=	19	19	19	29	29	29
Mean	7.78	8.29	0.52	7.57	7.67	0.10
2500mg						
N=	30	30	30	24	24	24
Mean	7.33	7.32	-0.02	7.45	8.06	0.61
Total						
N=	49	49	49	53	53	53
Mean	7.51	7.70	0.19*	7.51	7.85	0.33**

*P=0.3 **p=0.02

Mean body weight rose 0.5 kg with metformin XT (NS) and 1.3kg (p=0.007) for Glucophage. Mean BMI rose 0.2 with metformin XT (NS) and 0.5 (p=0.002) for Glucophage. Changes in serum lipids were small and there were no differences between the two arms.

The Sponsor was asked to perform an analysis of change in HbA1c in the subset of patients who were naïve to treatment. The purpose of this analysis was to isolate the glucose-lowering affect of study drug from changes in dosing of concomitant antidiabetic medications. As shown in the table below, Metformin XT was at least as effective as Glucophage in reducing HbA1c.

Treatment-naïve Patients, ITT

	Metformin XT n=11			Glucophage n=11		
2000mg						
N=	4	4	4	6	6	6
Mean	8.30	7.60	-0.70	7.92	7.40	-0.52
2500mg						
N=	7	7	7	5	5	5
Mean	6.83	6.36	-0.47	7.36	7.28	-0.08
Total						
N=	11	11	11	11	11	11
Mean	7.36	6.81	-0.55	7.66	7.35	-0.32

Study 303 – Placebo-controlled trial

This was a 4 month trial to compare maximum dose Metformin XT to placebo in patients with type 2 diabetes who were naïve to treatment or had been off antidiabetic medications at least 8 weeks. To be randomized, eligible patients had to have HbA1c at visit 1 of 7.5% or greater and FPG 150-240 mg/dl. Dosing began with one 1000-mg tablet given with the evening meal. The dose was increased by 500 mg weekly until the maximal dose of 2500mg (2x 1000 mg tablet plus 500mg tablet) was achieved. Patients who could not tolerate 2500 mg were allowed to drop back to 2000 mg and then to 1500 mg. Patients who could not tolerate 1500 mg by week four were withdrawn. Study drugs were 500 mg and 1000mg tablets of metformin XR or matching placebo, all doses given once daily Immediately after the evening meal.

At week 8 and beyond patients were withdrawn if:

FPG>200 mg/dl with <20mg/dl fall from baseline

or if HbA1c>11% at any time.

Of randomized patients, 55% were male, 64% white, 18% black and 18% Hispanic. The mean age was 56 years, mean weight 87 kg, mean BMI 30%. The maximum tolerated dose was 2500 mg for 64% of Metformin XR patients and 94% of placebo patients, 2000 mg and 1500 mg for 9% and 14% of Metformin XR patients. Missing information accounted for 14% of Metformin XR patients and 6% of placebo patients.

Results

Change in HbA1c:

As shown in the table below, the placebo subtracted LS mean change for HbA1c in the ITT population was -0.78 (p=0.028).

Change in HbA1c baseline to endpoint ITT

Treatment	N	Baseline, mean	Endpoint, mean	Change
Metformin XT	19	8.54	7.28	-1.26
Placebo	33	8.65	8.23	-0.43

For the per protocol population, the placebo subtracted LS mean change for HbA1c was -0.76 (p=0.028).

Change in HbA1c baseline to endpoint per-protocol

Treatment	N	Baseline, mean	Endpoint, mean	Change
Metformin XT	16	8.41	7.24	-1.17
Placebo	27	8.66	8.23	-0.43

Of 22 patients randomized to Metformin XR, one patient (4%) withdrew because of lack of efficacy. Of 34 patients randomized to placebo, 12 patients (35%) withdrew because of lack of efficacy. There was a statistically significant difference ($p=0.0087$) in the distribution of time to discontinuation due to lack of therapeutic response between the two groups.

Changes in other efficacy measures for the ITT population are shown in the tables below:

Fasting Plasma Glucose, mg/dl				
Metformin XT	193	149	-44	-39 ($p=0.026$)
Placebo	193	189	-4	
Fasting Plasma Insulin uU/ml				
Metformin XT	11	8.6	-2.3	-1.1 (NS)
Placebo	13	11	-1.7	
Fructosamine, umol/L				
Metformin XT	353	298	-55	-44 ($p=0.036$)
Placebo	374	361	-13	

Lipid Parameters

	Baseline, mean	Endpoint	Percent Change	
			Mean	Median
Cholesterol, mg/dl				
Metformin XT	209	197	-5.6	-3.0
Placebo	223	219	-17	-2.5
LDL, cholesterol				
Metformin XT	116	107	-5.7	-7.9
Placebo	129	128	0.1	-1.3
HDL, cholesterol				
Metformin XT	46	45	-2.3	-3.5
Placebo	51	48	-5.5	-9.3
Triglycerode, mg/dl				
Metformin XT	265	238	6.3	2.2
Placebo	212	243	10.2	-0.7

Change in Body Weight, baseline to endpoint ITT

Treatment	Baseline, mean	Endpoint, mean	Change
Metformin XT	81.6	81.0	-0.7
Placebo	93.2	91.6	-1.6

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Discussion of Efficacy:

Fortamet (Metformin XT) was developed to be used in place of Glucophage with the advantage that it requires only once a day dosing. Given that the Sponsor proposes to duplicate most of the text of the Glucophage label, it is reasonable to require that Metformin XT be therapeutically equivalent to Glucophage. The pivotal trial, trial 301, showed that Metformin XT was non-inferior to Glucophage based on the pre-specified method of statistical analysis, using a non-inferiority margin of 0.4% for HbA1c reduction. However, a direct comparison of the mean changes showed that Metformin XT was inferior statistically to Glucophage. Thus, the choice of a non-inferiority margin of 0.4% was critical.

It would be incorrect to conclude that FDA considers a difference of 0.4% units in HbA1c to be clinically insignificant. The non-inferiority margin of 0.4% units can be justified as follows:

- 1 FDA considers two formulations of the same drug to be bioequivalent if the confidence intervals of the relative bioavailability falls between 80-125%. The relative bioequivalence need not be 100%. In other words, if B is less bioavailable than A, but the confidence interval of the difference does not exceed **20%**, B is close enough to A to be considered bioequivalent.
- 2 Use of metformin monotherapy in patients with untreated diabetes has generally resulted in a reduction in HbA1c of about **2% units**.
- 3 The non-inferiority margin of 0.4% units can arise from combining the information in #1 and #2: **20% x 2% units = 0.4% units**. In other words, if one formulation of metformin could be expected to lower HbA1c from 9% to 7% (reduction of 2 % units), a second preparation would be approvable, if it were expected to lower HbA1c from 9% to <7.4 (reduction of >1.6% units).*

* per Dr Sahlroot – The actual mean reduction would be greater than 1.6% units since the mean treatment difference in the change from baseline must be sufficiently smaller than 0.4% so that the upper bound of the 95% CI for the difference does not exceed 0.4%.

Metformin XT might not be quite as efficacious as Glucophage, but it is close enough to be useful clinically, particularly because it requires less frequent dosing. However, this reasoning is open to challenge. Unlike the situation cited above (reduction by metformin in HbA1c from 9% to 7%), the mean HbA1c levels in trial 301 actually rose in both arms. This observation led Dr Sahlroot to question the assay sensitivity of the trial. His point is well taken. How can one be sure that the patients in this trial were responsive to metformin at all? What is the evidence that Metformin XT can actually lower HbA1c levels?

This problem is solved at least partially by consideration of data from trials 302 in which Metformin XT lowered HbA1c levels in the treatment-naïve patients to at least the same extent as did Glucophage. However, there were very few naïve patients in this trial so the power to detect a difference is small.

Addition data comes from the four month placebo controlled trial 303. This trial showed that Fortamet reduced mean HbA1c levels from 8.54% to 7.28% compared to a reduction from 8.65 to 8.23% for placebo.

When all the efficacy data are taken together, I believe the Sponsor has shown that Fortamet is effective in lowering HbA1c levels and that the efficacy of Fortamet given once daily is close enough to that of Glucophage twice daily, that the two treatment regimens can probably be used interchangeably in most patients. The most meaningful way to note the difference is that 2% of patients on Glucophage in trial 301 withdrew because of “lack of efficacy” compared to 5% of Fortamet ($p=0.047$).

V11 Review of Safety:

Study 301:

One patient on Metformin XT died. This patient had an incarcerated umbilical hernia on day 135, developed pneumonia and died. A serious AE was reported by 5.1% of patients on Metformin XT and 4.7% on Glucophage. Withdrawals due to AE occurred in 5.1% of patients on Metformin XT and 4.5% of patients on Glucophage. In 6/17 patients on Metformin XT and 10/15 Glucophage, the withdrawals were due to gastrointestinal complaints thought to be possible related to study drug.

Treatment-emergent signs and symptoms were reported by 74% of patients on Metformin XT and 73.6% of patients on Glucophage. Complaints in the gastrointestinal system were 33.4% (diarrhea 16.7%) on Metformin XT and 30.6 (diarrhea 13.1%) on Glucophage. 6/335 of patients on Glucophage XT experienced hypoglycemia and 7/337 on Glucophage. All but one in each arm was taking other antidiabetic agents in addition to study drug. One patient (028-032) on Metformin XT was withdrawn because of hypoglycemia.

Study 302:

One patient on Metformin XT died. The patient had a long history of coronary artery disease and was found unresponsive one morning. Treatment-emergent signs and symptoms were reported by 80% of patients on Metformin XT and 66% on Glucophage. Complaints in the gastrointestinal system were reported in 17/54 (31%) with Metformin XT and 14/59(14%) of patients on Glucophage. Diarrhea was reported in 10/54 (19%) with Metformin XT and 6/59(10%) of patients on Glucophage. Complaints in the gastrointestinal system led to no withdrawals from Metformin XT and 3 withdrawals from Glucophage.

Study 303:

There were no deaths or drug-related SAE's. About 10% of patients in each group withdrew because of AE's that were thought to be possibly drug related. There were two patients in each group that withdrew because of gastrointestinal complaints. In the two Metformin XT patients the complaints were diarrhea and flatulence. In the two placebo patients the complaints were diarrhea and "stomach" cramps. Gastrointestinal complaints were reported in 13/21 (62%) patients on Metformin XT compared to 9/34 (27%) patients on placebo. Mean hematocrit fell from 44.9 to 43.5 in patients on metformin XT and remained unchanged at 42.9 in patients on placebo.

A 120 day safety update submitted April 16, 2003 contains no information that would affect the labeling or use of this product.

VIII Dosing and Administration Issues

The label recapitulates the safety and efficacy data from the Glucophage label. This is acceptable because the clinical studies have demonstrated that Fortamet and Glucophage are therapeutically equivalent or nearly so. Suggested changes for the label are given in an appendix to be communicated to the Sponsor. Of particular importance is the suggestion by Dr Sahlroot that the greater withdrawal rate for "lack of efficacy" be communicated in the label.

Laura Pincock of DDMAC has suggested several changes be made in the PPI. I have included these in an appendix – "To be communicated to the Sponsor"

IX Use in Special Populations – No issues pertain

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X Conclusions and Recommendations:

The efficacy of Metformin XT given once daily is close enough to that of Glucophage twice daily, that the two treatment regimens can probably be used interchangeably in most patients.. To the extent that Glucophage may be slightly more effective than Metformin XT, patients may be able to compensate by increasing the dose of Metformin XT. This shortcoming of Metformin XT is potentially offset by the convenience of once a day dosing. The safety profile of Metformin XT and Glucophage are similar.

The application contains serious deficiencies regarding biopharmacy issues. Among these is lack of a dose-equivalency study (2x 500mg = 1x 1000 mg tablet) for the to-be-marketed formulation. These deficiencies are discussed in Dr Wei's review.

It would be desirable to market 500-mg and 1000 mg tablets, especially for naïve patients for whom titration by 500 mg increments may sometimes be desirable. But 1000 mg of Glucophage twice daily is a regimen used currently by many patients. For them, Fortamet given once daily (2x 1000 mg tablets) would be a convenient alternative.

The label for Fortamet should be similar to that of Glucophage. The proposed label is highly promotional and needs to be revised as described in the appendix .

Recommendation:

The 1000-mg tablet can be approved provided that changes are made to the proposed label. The 500 mg tablet should not be approved until bioequivalence (2x 500mg = 1x 1000 mg tablet) has been established

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/s/

Robert Misbin
2/20/04 10:13:01 AM
MEDICAL OFFICER

David Orloff
2/20/04 10:18:06 AM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

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

APPLICATION #: 21574 APPLICATION TYPE: NDA.....
SPONSOR: ANDRX PROPRIETARY NAME: Metformin XT.....
CATEGORY OF DRUG: Antidiabetic USAN / Established Name: Fortamet.....
ROUTE: Oral.....
MEDICAL REVIEWER: Robert I Misbin.. REVIEW DATE: October 8, 2003.....

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
Dec 19, 2002	Dec 23, 2002		
April 16, 2003	April 17, 2003	Safety update	

Metformin XT once daily is nearly as effective in lowering HbA1c levels as Glucophage twice daily. This shortcoming of Metformin XT is potentially offset by the convenience of once a day dosing. The safety profile of Metformin XT and Glucophage are similar. Because dose equivalency (2x 500mg=1x1000mg) has not been established, only the 1000 mg tablet should be approved at present.

The 1000-mg tablet can be approved provided that changes are made to the proposed label.

Signed: Medical Reviewer: Robert I Misbin MD Date: Oct 14, 2003

Medical Team Leader: _____ Date: _____

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Executive Summary

I Recommendations:

The efficacy of Metformin XT given once daily is close enough to that of Glucophage twice daily, that the two treatment regimens can probably be used interchangeably in most patients. This shortcoming of Metformin XT is potentially offset by the convenience of once a day dosing. The safety profile of Metformin XT and Glucophage are similar. Because dose equivalency (2x 500mg=1x1000mg) has not been established, only the 1000 mg tablet should be approved at present.

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II Summary of Clinical Findings

Metformin XT is a long acting preparation of metformin to be marketed under the trade name, Fortamet. It was designed to be given once daily and achieve the same glucose control as immediate release Metformin given twice daily. The Sponsor performed three phase 3 trials. Two of these were comparisons to immediate release Metformin (Glucophage) and the third was a placebo-controlled study.

Study 301 was designed to demonstrate the non-inferiority of Fortamet given once daily at dinner to Glucophage give twice daily in patient who had been taking Glucophage for at least 12 weeks. As shown in the table, mean HbA1c rose in both groups. Using a non-inferiority margin of 0.4% units for change in HbA1c, Fortamet was non-inferior to Glucophage with respect to maintaining glucose control. The safety/tolerability profile of Fortamet and Glucophage were similar.

Mean HbA1c study 301.

	N (ITT)	Baseline	Endpoint	Change	Difference
Met XT	313	7.02	7.42	0.40	0.27
Glucophage	322	7.08	7.21	0.13	

Study 302 was done to study safety. Its design was similar to study 301 except that there was a forced to titration to 2000 mg or 2500 mg (the maximal labeled dose of metformin). As was the case with trial 301, mean HbA1c levels rose somewhat but the rise was similar on both drugs (see table below).

	Metformin XT			Glucophage		
N=	49	49	49	53	53	53
Mean	7.51	7.70	0.19	7.51	7.85	0.33

The Sponsor was asked to perform an analysis of change in HbA1c in the subset of patients who were naïve to treatment. The purpose of this analysis was to isolate the glucose-lowering affect of study drug from changes in dosing of concomitant antidiabetic medications. As shown in the table below, Metformin XT was about as effective as Glucophage in reducing HbA1c.

HbA1c: Treatment-naïve Patients, ITT

	Metformin XT n=11			Glucophage n=11		
2000mg						
N=	4	4	4	6	6	6
Mean	8.30	7.60	-0.70	7.92	7.40	-0.52
2500mg						
N=	7	7	7	5	5	5
Mean	6.83	6.36	-0.47	7.36	7.28	-0.08
Total						
N=	11	11	11	11	11	11
Mean	7.36	6.81	-0.55	7.66	7.35	-0.32

Study 303 was a four month, double-blind, placebo-controlled trial in patients who were naïve to pharmacologic treatment or had been off antidiabetic medication at least 8 weeks. As shown in the table below, the placebo subtracted LS mean change for HbA1c in the ITT population was -0.78 (p=0.028).

Change in HbA1c baseline to endpoint ITT

Treatment	N	Baseline, mean	Endpoint, mean	Change
Metformin XT	19	8.54	7.28	-1.26
Placebo	33	8.65	8.23	-0.43

The safety/tolerability profile of Metformin XT was similar to what has been found with immediate release metformin.

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Metformin (Glucophage) has been available in the USA since 1995 and is generally considered the treatment of choice for obese patients with type 2 diabetes. It can be used as monotherapy or in combination with other antidiabetic agents including insulin.

Metformin (Glucophage) is given twice or three times per day in doses ranging from 500 mg bid to 850 mg tid. Gastrointestinal discomfort occurs early in treatment and is the major limiting factor in dose escalation. Most patients can tolerate or become tolerant to the gastrointestinal AE's of metformin. A regimen of 1000 mg bid is common. Glucophage is marketed as 500 mg, 850 mg and 1000 mg tablets. Generic metformin is also available.

Glucophage XR is a once a day preparation of metformin. It is marketed as 500 mg and 750 mg tablets. The maximum recommended dose of Glucophage XR is 2000 mg once daily with the evening meal.

Metformin XT is a long acting preparation of metformin to be marketed under the trade name, Fortamet. It was designed to be given once daily and achieve the same glucose control as immediate release Metformin given twice daily. The Sponsor performed three phase 3 trials. Two of these were comparisons to immediate release Metformin (Glucophage) and the third was a placebo-controlled study.

II Clinically relevant findings from review from other disciplines

Commenting on the efficacy results (HbA1c reduction) from trial 303, the statistical reviewer, Dr Todd Sahlroot, notes:

“Because the lower bound of the CI for the mean difference excluded zero, XT was also statistically inferior to Glucophage ($p < 0.0001$) in addition to being clinically non-inferior”.

This result arises from the use of a non-inferiority margin of 0.4% for the change in HbA1c.

Dr Sahlroot noted that dropouts due to “lack of efficacy” were 5% of XT patients compared to 2% of Glucophage patients ($p = 0.047$)

Dr Sahlroot also questions the “assay sensitivity” of the trial, noting that mean HbA1c levels rose from baseline to endpoint in both treatment arms.

These issues are dealt with in the “Discussion of efficacy” section of this review.

III Pharmacokinetic and Pharmacodynamics Issues:

There are two major PK issues:

The dosage equivalence between the 500 mg and 1000 mg tablets has not been established for the phase 3 and commercial formulations. Indeed, the dose equivalence study of the pilot lot failed.

The PK/relative bioavailability information in the proposed label was derived from studies using the pilot lot and the pilot lots and phase 3 lots were not bioequivalent.

These problems are discussed in Dr Wei's review. From a clinical perspective, I offer the following comments:

Fortamet given once daily is nearly as effective as Glucophage given twice daily. Both preparations of Metformin (Glucophage and Fortamet) show decreasing absorption with increasing dose. This explains, in my judgment, why 1000 mg of Glucophage given twice daily is somewhat more effective than 2000 mg of Fortamet given once daily.

The efficacy of the 1000 mg dose of Fortamet has been established by the clinical trials. But the efficacy of the 500 mg dose of Fortamet has not established by the clinical trials. The 500 mg tablet was always given along with one or two 1000 mg tablets. Given the size of the trials, and variability of response, one cannot expect to distinguish 1000 mg from 1500 mg or 2000 mg from 2500 mg. The 500 mg tablet was never used alone. Therefore, its efficacy has not been established.

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IV Description of Clinical Sources
(See clinical review)

V Clinical Review Methods:

The review was conducted of the hard copy of the summary of the NDA with reference to other documents that had been submitted electronically. No routine inspections of the sites were performed. Although the consent documents were not reviewed, the trials appears to have been conducted in accordance with acceptable ethical standards. The escape criteria for lack of efficacy are praiseworthy. The financial disclosure documentation appears adequate.

Regulatory statements regarding documents reviewed:

The Sponsor, Andrx Labs submitted debarment and financial disclosure documents. The documents are signed by Nicholas Farina, Vice President of Andrx Labs on 11/20/02. I have examined these documents and found them to be acceptable. The debarment statement indicated that the Andrx Labs did not and will use the services of any individual or organization that had been debarred.

The Sponsor makes reference to FDA form 3455. The following financial disclosure information has been submitted:

- 1 Form OMB No. 0910-0396. The applicant certifies that Andrx Labs 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 Andrx Labs
- 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 Andrx Labs.
- 4 List of investigators from whom completed financial disclosure forms were received.

VI Review of Efficacy

Study 301

This was a double-blind study to evaluate Metformin XT once daily vs Glucophage twice daily in patients with type 2 diabetes who had previously been taking Metformin. A double-dummy design was used to maintain the blind so that each patient received both active drug and placebo for the alternative medication. Metformin XT (or placebo) was given once daily at about 6:00 PM before dinner. Glucophage (or placebo) was given at about 8:00 am before breakfast and 6:00 pm. Eligible patients were to have been on a stable dose of Metformin for at least 12 weeks. For the first 6 weeks, the dose of study medication was titrated to achieve a FPG of 140 mg/dl. For the last 20 weeks the dose was kept constant. Other antidiabetic medications could be continued during the trial at their pre-trial dose.

Inclusion criteria: Patients had type 2 diabetes, 30-70 years of age on a fixed dose of Glucophage 850 to 2550 mg/d for at least 12 weeks. At visit 1 (screening), HbA1c was 9% or less, FPG < 230 mg/dl. Difference in FPG between visits 1 and 2 could not exceed 20% of the higher value. In addition to the standard exclusion criteria, patients could not be using a glitazone in combination with metformin.

Dosing: Randomization and dosing began at visit 3 (2 weeks after screening). Dosing was initiated based on the previous dose of metformin and the FPG. The dose was titrated in an attempt to achieve a FPG of 140 mg/dl. The minimal dose was 1000 mg/d and the maximal dose was 2500. Study medications were administered as 500 mg or 1000 mg tablets or matching placebos. Doses of 1000 mg and 2000 mg were given as 1x or 2x 1000 mg tablets. The dose of 1500 mg or 2500 mg were achieved by adding a single 500 mg tablet. No change in study medication dose was allowed beyond week 6.

Hypothesis and level of significance: The study was designed to support approval for Metformin XT with the same indications as Glucophage. Metformin XT was required to pass a non-inferiority test vs Glucophage using HbA1c, with a non-inferiority margin of 0.4 and 80% power.

Disposition:

680 patients were randomized. 263/339 (77.6%) of patients randomized to Metformin XT completed the trial compared to 292/341 (84.2%) of patients randomized to Glucophage. 18/339 (5.3%) of patients randomized to Metformin XT withdrew because of **“lack of efficacy”** compared to 8/341 (2.3%) of patients randomized to Glucophage.

Demography:

Patients were 59% male, 75% white, 14% Hispanic and 9% black. The mean age was about 57 years. The mean weight was about 95kg, mean BMI 31.4 The distribution of metformin dose at randomization was < 1500 mg (33%), 1500-<2000mg (19%), 2000 mg or more (48%). Approximately 50% of patients were using insulin secretagogues (mainly Glyburide and Glipizide). Approximately 7% were using insulin. Approximately 40% were using lipid-lowering drugs or ACE inhibitors. About 16 % were using beta blockers. The two arms appeared to be well matched with respect to demographic characteristics.

The dose of study medication at the end of the titration period is in the following table:
% of all randomized patients

Final dose	Metformin XT	Glucophage
1000mg	12.7	10.3
1500mg	8.0	12.9
2000mg	23.6	19.1
2500mg	55.8	57.8

The average final dose was 2119 for Met XT and 2126 for Glucophage. The mean change from baseline was 443 for Metformin XT and 467 for Glucophage.

Result:

	N (ITT)	Mean HbA1c			
		Baseline	Endpoint	Change	Difference
Met XT	313	7.02	7.42	0.40	0.27
Glucophage	322	7.08	7.21	0.13	

From the table shown above, it appears that Met XT and Glucophage were approximate the same in maintaining HbA1c levels. Values rose slightly in both groups. Based on a non-inferiority margin of 0.4%, Met XT passed a test of non-inferiority but only barely. The upper limit of the 97.5% CI for the difference in HbA1c at endpoint is 0.385.

The change in HbA1c based on baseline dose is displayed in the following table. Not unexpectedly, patients taking larger doses of drug at baseline had higher HbA1c levels and the increase at endpoint tended to be greater as well. One notes however, that the rise in HbA1c in patients on Glucophage did not occur in patients taking less than 2000mg per day. By contrast, the rise in HbA1c occurred at all dose levels for patients taking Metformin XT, although it was greatest at the highest dose level.

	Metformin XT				Glucophage		
1000	6.85	7.14	0.29		6.95	6.97	0.02
1500	6.81	7.07	0.26		7.09	7.03	-0.06
2000	7.12	7.57	0.45		7.08	7.25	0.17
2500	7.39	8.09	0.70		7.47	7.93	0.46

As shown in the table that follows the result using the per protocol population was largely the same as with the ITT population. For the per protocol population, the upper limit of the 97.5% CI for the difference in HbA1c at endpoint is 0.300

	N(per protocol)	Mean HbA1c			
		Baseline	Endpoint	Change	Difference
Met XT	255	6.97	7.29	0.32	0.18
Glucophage	287	7.05	7.18	0.13	

In the ITT population, the mean FPG at baseline was about 146 mg/dl in both groups. It rose at endpoint by 10.0 mg/dl with Metformin XT and 4.2 mg/dl with Glucophage. The difference of the LS mean increase was 6.43 mg/dl (95% CI 0.6-12.2). The p value for this difference is 0.03

In the ITT population, the mean fructosamine at baseline was about 290 umol/L in both groups. It rose at endpoint by 16.9 with Metformin XT and 2.3 with Glucophage. The difference of the LS mean increase was 15.5 (95% CI 9.6-21.4). The p value for this difference is 0.0001

Mean fasting plasma insulin levels were about 17.5 uU/ml at baseline and fell about 3.5 uU/ml in both groups. In the PP population, the mean FPG at baseline was about 145 mg/dl in both groups. It rose at endpoint by 6.0 mg/dl with Metformin XT and 2.9 mg/dl with Glucophage. The difference of the LS mean increase was 3.04 mg/dl (95% CI – 2.7, 8.8).

In the PP population, the mean fructosamine at baseline was about 289 umol/L in both groups. It rose at endpoint by 11.6 with Metformin XT and 2.1 with Glucophage. The difference of the LS mean increase was 15.5 (95% CI 3.8, 15.7).

Mean body weight at baseline was about 94 kg. The change was +0.3 kg (95% CI 0.0, 0.6) for Metformin XT and 0.0 kg for Glucophage. BMI was about 31.2. The change was +0.1(95% CI 0.0, 0.2) for Metformin XT and 0.0 for Glucophage.

Lipid levels changed little during the trial. The only value possibly worth noting is a rise in triglyceride from 199 to 246 in patients on Metformin XT. In patients on Glucophage, mean triglyceride levels remained unchanged at 200 mg/dl.

Study 302 – To compare the tolerability and safety of 2000 mg and 2500 mg Metformin XT given once daily to the same dose of Glucophage given twice daily.

This was a double-blind study to evaluate Metformin XT once daily vs Glucophage twice daily when given in doses of 2000 mg or 2500 mg per day. A double-dummy design was used to maintain the blind so that each patients received both active drug and placebo for the alternative medication. Metformin XT (or placebo) was given once daily at about 6:00 pm before dinner. Glucophage (or placebo) was given at about 8:00 am before breakfast and 6:00 pm. “Patients were assigned to either 2000mg or 2500mg as needed in order to achieve at least 100 in each of these high dose groups between the two protocols (301 and 302)”. 56 patients were randomized to Metformin XT and 59 were randomized to Glucophage.

Patients on 1000 mg or less of metformin received 1000 mg initially which was increased to the assigned 2000 or 2500 mg at the rate of 500 mg per week. Patients on 2000 mg or more received their assigned dose of 2000 mg or 2500 mg initially and throughout. Patients on between 1000-2000 mg received 1500-2000mg initially which was increased to the assigned 2000 or 2500 mg. During the first 4 weeks, the dose of any concomitant antidiabetic medication was adjusted at the discretion of the investigator in order to allow for the “protocol-driven” increases to the assigned dose of either 2000 or 2500mg.

Inclusion criteria: Patients had type 2 diabetes, 30-70 years of age HbA1c was 9% or less, FPG < 230 mg/dl.

Statistics: The study was designed to compare the safety of high dose Metformin XT with the same dose as Glucophage. There was no power calculation

Demography:

Patients were about 67% male, 63% white, 23% Hispanic and 13% black. The mean age was about 55 years. The mean weight was about 93kg, mean BMI 31. 68% of patients on Metformin XT and 78% on Glucophage were using insulin secretagogues (mainly Glyburide and Glipizide). Approximate 15% were using insulin. 14/56 patients randomized to Metformin XT and 11/59 patients randomized to Glucophage were receiving no antidiabetic medications. 78% of patients randomized to Metformin XT and 70% of patients randomized to Glucophage had no change in their concomitant antidiabetic medications during the trial (this includes the patients who were taking no antidiabetic medications other than study drugs). Of the patients who did have changes in their other medications, there appeared to be no difference between the two arms with respect to adding new medications, dropping old ones, or changes in dose.

Results:

As shown in the table below, HbA1c values tended to rise over the study but there was no difference between Metformin XT and Glucophage. This result was mirrored in change in FPG, which rose 14 mg/dl in both groups, 152 mg/dl to 166 mg/dl for Metformin XT (p=0.02), and 150 to 164 (p=0.02) for Glucophage.

	Metformin XT			Glucophage		
2000mg						
N=	19	19	19	29	29	29
Mean	7.78	8.29	0.52	7.57	7.67	0.10
2500mg						
N=	30	30	30	24	24	24
Mean	7.33	7.32	-0.02	7.45	8.06	0.61
Total						
N=	49	49	49	53	53	53
Mean	7.51	7.70	0.19*	7.51	7.85	0.33**

*P=0.3 **p=0.02

Mean body weight rose 0.5 kg with metformin XT (NS) and 1.3kg (p=0.007) for Glucophage. Mean BMI rose 0.2 with metformin XT (NS) and 0.5 (p=0.002) for Glucophage. Changes in serum lipids were small and there were no differences between the two arms.

The Sponsor was asked to perform an analysis of change in HbA1c in the subset of patients who were naïve to treatment. The purpose of this analysis was to isolate the glucose-lowering affect of study drug from changes in dosing of concomitant antidiabetic medications. As shown in the table below, Metformin XT was at least as effective as Glucophage in reducing HbA1c.

Treatment-naïve Patients, ITT

	Metformin XT n=11			Glucophage n=11		
2000mg						
N=	4	4	4	6	6	6
Mean	8.30	7.60	-0.70	7.92	7.40	-0.52
2500mg						
N=	7	7	7	5	5	5
Mean	6.83	6.36	-0.47	7.36	7.28	-0.08
Total						
N=	11	11	11	11	11	11
Mean	7.36	6.81	-0.55	7.66	7.35	-0.32

This was a 4 month trial to compare maximum dose Metformin XT to placebo in patients with type 2 diabetes who were naïve to treatment or had been off antidiabetic medications at least 8 weeks. To be randomized, eligible patients had to have HbA1c at visit 1 of 7.5% or greater and FPG 150-240 mg/dl. Dosing began with one 1000-mg tablet given with the evening meal. The dose was increased by 500 mg weekly until the maximal dose of 2500mg (2x 1000 mg tablet plus 500mg tablet) was achieved. Patients who could not tolerate 2500 mg were allowed to drop back to 2000 mg and then to 1500 mg. Patients who could not tolerate 1500 mg by week four were withdrawn. Study drugs were 500 mg and 1000mg tablets of metformin XR or matching placebo, all doses given once daily immediately after the evening meal.

At week 8 and beyond patients were withdrawn if:

FPG>200 mg/dl with <20mg/dl fall from baseline

or if HbA1c>11% at any time.

Of randomized patients, 55% were male, 64% white, 18% black and 18% Hispanic. The mean age was 56 years, mean weight 87 kg, mean BMI 30%. The maximum tolerated dose was 2500 mg for 64% of Metformin XR patients and 94% of placebo patients, 2000 mg and 1500 mg for 9% and 14% of Metformin XR patients. Missing information accounted for 14% of Metformin XR patients and 6% of placebo patients.

Results

Change in HbA1c:

As shown in the table below, the placebo subtracted LS mean change for HbA1c in the ITT population was -0.78 (p=0.028).

Change in HbA1c baseline to endpoint ITT

Treatment	N	Baseline, mean	Endpoint, mean	Change
Metformin XT	19	8.54	7.28	-1.26
Placebo	33	8.65	8.23	-0.43

For the per protocol population, the placebo subtracted LS mean change for HbA1c was -0.76 (p=0.028).

Change in HbA1c baseline to endpoint per-protocol

Treatment	N	Baseline, mean	Endpoint, mean	Change
Metformin XT	16	8.41	7.24	-1.17
Placebo	27	8.66	8.23	-0.43

Of 22 patients randomized to Metformin XR, one patient (4%) withdrew because of lack of efficacy. Of 34 patients randomized to placebo, 12 patients (35%) withdrew because

of lack of efficacy. There was a statistically significant difference ($p=0.0087$) in the distribution of time to discontinuation due to lack of therapeutic response between the two groups.

Changes in other efficacy measures for the ITT population are shown in the tables below:

Fasting Plasma Glucose, mg/dl				
Metformin XT	193	149	-44	-39 ($p=0.026$)
Placebo	193	189	-4	
Fasting Plasma Insulin uU/ml				
Metformin XT	11	8.6	-2.3	-1.1 (NS)
Placebo	13	11	-1.7	
Fructosamine, umol/L				
Metformin XT	353	298	-55	-44 ($p=0.036$)
Placebo	374	361	-13	

Lipid Parameters

	Baseline, mean	Endpoint	Percent Change	
			Mean	Median
Cholesterol, mg/dl				
Metformin XT	209	197	-5.6	-3.0
Placebo	223	219	-17	-2.5
LDL, cholesterol				
Metformin XT	116	107	-5.7	-7.9
Placebo	129	128	0.1	-1.3
HDL, cholesterol				
Metformin XT	46	45	-2.3	-3.5
Placebo	51	48	-5.5	-9.3
Triglycerode, mg/dl				
Metformin XT	265	238	6.3	2.2
Placebo	212	243	10.2	-0.7

Change in Body Weight, baseline to endpoint ITT

Treatment	Baseline, mean	Endpoint, mean	Change
Metformin XT	81.6	81.0	-0.7
Placebo	93.2	91.6	-1.6

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Discussion of Efficacy:

Fortamet (Metformin XT) was developed to be used in place of Glucophage with the advantage that it requires only once a day dosing. Given that the Sponsor proposes to duplicate most of the text of the Glucophage label, it is reasonable to require that Metformin XT be therapeutically equivalent to Glucophage. The pivotal trial, trial 301, showed that Metformin XT was non-inferior to Glucophage based on the pre-specified method of statistical analysis, using a non-inferiority margin of 0.4% for HbA1c reduction. However, a direct comparison of the mean changes showed that Metformin XT was inferior statistically to Glucophage. Thus, the choice of a non-inferiority margin of 0.4% was critical.

It would be incorrect to conclude that FDA considers a difference of 0.4% units in HbA1c to be clinically insignificant. The non-inferiority margin of 0.4% units can be justified as follows:

- 1 FDA considers two formulations of the same drug to be bioequivalent if the confidence intervals of the relative bioavailability falls between 80-125%. The relative bioequivalence need not be 100%. In other words, if B is less bioavailable than A, but the confidence interval of the difference does not exceed 20%, B is close enough to A to be considered bioequivalent.
- 2 Use of metformin monotherapy in patients with untreated diabetes has generally resulted in a reduction in HbA1c of about 2% units.
- 3 The non-inferiority margin of 0.4% units can arise from combining the information in #1 and #2: $20\% \times 2\% \text{ units} = 0.4\% \text{ units}$ In other words, if one formulation of metformin could be expected to lower HbA1c from 9% to 7% (reduction of 2 % units), a second preparation would be approvable, if it were expected to lower HbA1c from 9% to <7.4 (reduction of >1.6% units).*

* per Dr Sahlroot – The actual mean reduction would be greater than 1.6% units since the mean treatment difference in the change from baseline must be sufficiently smaller than 0.4% so that the upper bound of the 95% CI for the difference does not exceed 0.4%.

Metformin XT might not be quite as efficacious as Glucophage, but it is close enough to be useful clinically, particularly because it requires less frequent dosing. However, this reasoning is open to challenge. Unlike the situation cited above (reduction by metformin in HbA1c from 9% to 7%), the mean HbA1c levels in trial 301 actually rose in both arms. This observation led Dr Sahlroot to question the assay sensitivity of the trial. His point is well taken. How can one be sure that the patients in this trial were responsive to metformin at all? What is the evidence that Metformin XT can actually lower HbA1c levels?

This problem is solved at least partially by consideration of data from trials 302 in which Metformin XT lowered HbA1c levels in the treatment-naïve patients to at least the same extent as did Glucophage. However, there were very few naïve patients in this trial so the power to detect a difference is small.

Addition data comes from the four month placebo controlled trial 303. This trial showed that Fortamet reduced mean HbA1c levels from 8.54% to 7.28% compared to a reduction from 8.65 to 8.23% for placebo.

When all the efficacy data are taken together, I believe the Sponsor has shown that Fortamet is effective in lowering HbA1c levels and that the efficacy of Fortamet given once daily is close enough to that of Glucophage twice daily, that the two treatment regimens can probably be used interchangeably in most patients. The most meaningful way to note the difference is that 2% of patients on Glucophage in trial 301 withdrew because of "lack of efficacy" compared to 5% of Fortamet (p=0.047).

V11 Review of Safety:

Study 301:

One patient on Metformin XT died. This patient had an incarcerated umbilical hernia on day 135, developed pneumonia and died. A serious AE was reported by 5.1% of patients on Metformin XT and 4.7% on Glucophage. Withdrawals due to AE occurred in 5.1% of patients on Metformin XT and 4.5% of patients on Glucophage. In 6/17 patients on Metformin XT and 10/15 Glucophage, the withdrawals were due to gastrointestinal complaints thought to be possible related to study drug.

Treatment-emergent signs and symptoms were reported by 74% of patients on Metformin XT and 73.6% of patients on Glucophage. Complaints in the gastrointestinal system were 33.4% (diarrhea 16.7%) on Metformin XT and 30.6 (diarrhea 13.1%) on Glucophage. 6/335 of patients on Glucophage XT experienced hypoglycemia and 7/337 on Glucophage. All but one in each arm was taking other antidiabetic agents in addition to study drug. One patient (028-032) on Metformin XT was withdrawn because of hypoglycemia.

Study 302:

One patient on Metformin XT died. The patient had a long history of coronary artery disease and was found unresponsive one morning. Treatment-emergent signs and symptoms were reported by 80% of patients on Metformin XT and 66% on Glucophage. Complaints in the gastrointestinal system were reported in 17/54 (31%) with Metformin XT and 14/59(14%) of patients on Glucophage. Diarrhea was reported in 10/54 (19%) with Metformin XT and 6/59(10%) of patients on Glucophage. Complaints in the gastrointestinal system led to no withdrawals from Metformin XT and 3 withdrawals from Glucophage.

Study 303:

There were no deaths or drug-related SAE's. About 10% of patients in each group withdrew because of AE's that were thought to be possibly drug related. There were two patients in each group that withdrew because of gastrointestinal complaints. In the two Metformin XT patients the complaints were diarrhea and flatulence. In the two placebo patients the complaints were diarrhea and "stomach" cramps. Gastrointestinal complaints were reported in 13/21 (62%) patients on Metformin XT compared to 9/34 (27%) patients on placebo. Mean hematocrit fell from 44.9 to 43.5 in patients on metformin XT and remained unchanged at 42.9 in patients on placebo.

A 120 day safety update submitted April 16, 2003 contains no information that would affect the labeling or use of this product.

VIII Dosing and Administration Issues

The label recapitulates the safety and efficacy data from the Glucophage label. This is acceptable because the clinical studies have demonstrated that Fortamet and Glucophage are therapeutically equivalent or nearly so. Suggested changes for the label are given in an appendix to be communicated to the Sponsor. Of particular importance is the suggestion by Dr Sahlroot that the greater withdrawal rate for "lack of efficacy" be communicated in the label.

Laura Pincock of DDMAC has suggested several changes be made in the PPI. I have included these in an appendix – "To be communicated to the Sponsor"

IX Use in Special Populations – No issues pertain

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X Conclusions and Recommendations:

The efficacy of Metformin XT given once daily is close enough to that of Glucophage twice daily, that the two treatment regimens can probably be used interchangeably in most patients.. To the extent that Glucophage may be slightly more effective than Metformin XT, patients may be able to compensate by increasing the dose of Metformin XT. This shortcoming of Metformin XT is potentially offset by the convenience of once a day dosing. The safety profile of Metformin XT and Glucophage are similar.

The application contains serious deficiencies regarding biopharmacy issues. Among these is lack of a dose-equivalency study (2x 500mg = 1x 1000 mg tablet) for the to-be-marketed formulation. These deficiencies are discussed in Dr Wei's review.

It would be desirable to market 500-mg and 1000 mg tablets, especially for naïve patients for whom titration by 500 mg increments may sometimes be desirable. But 1000 mg of Glucophage twice daily is a regimen used currently by many patients. For them, Fortamet given once daily (2x 1000 mg tablets) would be a convenient alternative.

The label for Fortamet should be similar to that of Glucophage. The proposed label is highly promotional and needs to be revised as described in the appendix .

Recommendation:

The 1000-mg tablet can be approved provided that changes are made to the proposed label. The 500 mg tablet should not be approved until bioequivalence (2x 500mg = 1x 1000 mg tablet) has been established

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Appendix – Labeling revisions to be communicated to Sponsor:

PK section: Statements [] of Fortamet [] are promotional and should be deleted.

Study 302 was not powered to study efficacy. It was a safety study to compare near maximal doses of Fortamet and Metformin IR. [] Table 4 and the accompanying text should be deleted.

In study 301, significantly more patients on Metformin XT (5%) than Glucophage (2%) withdrew because of “lack of efficacy” (p=0.047). This should be stated in the label. Figure 2 is unnecessarily and should be deleted along with the explanatory text.

The statement that Fortamet did not cause weight gain repeats what is already in table 5. This statement should be deleted as well. Since there is no head to head comparison of Fortamet [] it is inappropriate to make a comparison regarding weight gain. Tables 6 and 7 should be deleted along with the explanatory text.

Indications:

The indications for Fortamet cannot go beyond the existing indications for Glucophage. [] should be deleted.

Adverse events:

The text under table 11 should give percentages of patients taking Fortamet and Metformin IR who reported flatulence, indigestion and abdominal pain/discomfort.

Dosage and Administration:

The statement [] should be deleted.

In PPI:

The statement [] is not correct. Either the statement should be deleted or the revised to say:

[]

The statements about hypoglycemia and weight gain should follow the Glucophage PPI. Hypoglycemia can be expected to occur when any form of metformin is given to patients on insulin or sulfonylureas.

The text is too promotional in tone and should be revised. The statement that Fortamet

J

Abdominal pain should be added to the list of common side effects

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David Orloff
10/16/03 06:39:34 PM
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MEDICAL OFFICER REVIEW

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

APPLICATION #:	21574	APPLICATION TYPE:	NDA.....
SPONSOR:	ANDRX	PROPRIETARY NAME:	Metformin XT.....
CATEGORY OF DRUG:	Antidiabetic	USAN / Established Name:	Fortamet.....
		ROUTE:	Oral.....
MEDICAL REVIEWER:	Robert I Misbin..	REVIEW DATE:	Feb12, 2003.....

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
Dec 19, 2002	Dec 23, 2002		

FILING MEMO

Signed: Medical Reviewer: Robert I Misbin MD Date: February 12, 2003

Medical Team Leader: _____ Date: _____

21574 Filing Memo

The NDA can be filed.

No advisory committee meeting is needed.

Two or three sites from study 302 should be inspected. The choice of sites can be left to the inspector.

Review issue:

For communication to Sponsor:

Although patients in study 302 received 2000 or 2500 mg of metformin as a new medication, the mean HbA1c level did not go down. Please submit HbA1c data (baseline, endpoint, and change for each patient and Mean \pm for each group) for the 14 treatment-naïve patients randomized to Metformin XT and the 11 treatment-naïve patients randomized to Glucophage.

We note lack of dosage equivalence between the 500 mg and 1000 mg tablets. Please provide additional information about which tablets were used at the various dose levels in the clinical trials, ie was 1500 mg given as 1000 mg + 500 mg or as 3 x 500mg?

Robert I Misbin MD
February 12, 2003

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MEDICAL OFFICER REVIEW

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

APPLICATION #: IND 55962..... **APPLICATION TYPE:** Commercial IND.....
SPONSOR: Aura Labs **PROPRIETARY NAME:** METFORMIN XT
CATEGORY OF DRUG: Antidiabetic **USAN / Established Name:** Metformin.....
ROUTE: Oral.....
MEDICAL REVIEWER: Robert I Misbin.. **REVIEW DATE:** March 18, 2002.....

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
March 12, 2002	March 13, 2001	Commercial IND	

Overview of Application/Review: The Sponsor plans to submitted an NDA for Metformin XT in the third quarter of 2002, and are requesting a deferral to satisfy the Pediatric Rule. After submission of the NDA, they propose to submit a protocol for a 24-week trial in children age 10-16 with type 2 diabetes designed to show non-inferiority of Metformin XT to Glucophage (immediate release metformin). Based on studies in adults, Metformin XT has a profile of safety and efficacy that is similar to Glucophage.

Recommendation: Grant the deferral of pediatric studies that the Sponsor requests.

Signed: Medical Reviewer: Robert I Misbin MD Date: March 18, 2002

Medical Team Leader: _____ Date: _____

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