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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

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. Appropropiate 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

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