

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-574

Chemistry Review(s)



NDA 21-574

Fortamet™ Extended-Release Tablets

Metformin HCl, USP ER Tablets

**Andrx Labs, Inc.
(Andrx)**

CMC Review # 2

**Xavier Ysern, PhD
HFD-510**



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CHEMISTRY REVIEW



Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. **NDA** 21-574
 2. **REVIEW #** 2
 3. **REVIEW DATE:** 01-AUG-2003 (review # 2)
 4. **REVIEWER:** Xavier Ysern

5. **PREVIOUS DOCUMENTS:** Document(s) Document Date
 -- --

6. **SUBMISSION(S) BEING REVIEWED:** Submission(s) Reviewed Document Date
 Original 17-DEC-2002
 Amendment 29-JAN-2003
 17-MAR-2003
 15-MAY-2003
 28-JUL-2003

7. **NAME & ADDRESS OF APPLICANT:**
Name: Andrx Labs, Inc. phone (201) 883-1898
Address: 401 Hackensack Avenue
 Hackensack, NJ 07601
Representative: Nicholas J. Farina, Vice President Regulatory Affairs
Telephone: (610) 428-2417 Fax: (201) 883-1893

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: Fortamet™ ER Tablets
 b) Non-Proprietary Name (USAN): Metformin HCl Extended-Release Tablets
 c) Code Name: --
 d) Chem. Type/Submission Priority:
 ▪ Chem. Type: Type 4
 ▪ Submission Priority: S

9. **LEGAL BASIS FOR SUBMISSION:** --

10. **PHARMACOLOGICAL CATEGORY:** Proposed for the treatment of Type 2 diabetes mellitus as an adjunct to diet and exercise

11. **DOSAGE FORM:** Tablets

12. **STRENGTH/POTENCY:** 500-mg and 1000-mg

13. **ROUTE OF ADMINISTRATION:** Oral

14. **Rx/OTC DISPENSED:** Rx

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):** Not a SPOTS product



CHEMISTRY REVIEW



Chemistry Review Data Sheet

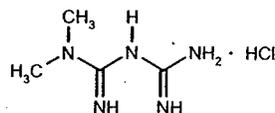
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WEIGHT:

Metformin Hydrochloride

$C_4H_{11}N_5 \cdot HCl$

MW = 129.17 + 36.46 = 165.63

CAS 657-25-9 (free base) 1115-70-4 (hydrochloride)



N,N-Dimethylimidodicarbonimidic diamine monohydrochloride or *N,N*-Dimethylbiguanide HCl

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	LOA date	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
Type II							
	05.Nov.2001		Metformin HCl (DS)	1	Adequate	23-JAN-2002	ANDA 75961
Type III							
	16.Mar.2001			4	Adequate		
	08.Oct.2002			4	Adequate		
	02.May.2002			4	Adequate		
	06.Aug.2002			4	Adequate		
	01.Mar.1999			4	Adequate		
	20.Dec.2001			3	Adequate	01-APR-1999	
	03.May.2000			4	Adequate		
	25.May.2001			4	Adequate		
	02.May.2002			4	Adequate		
	07.Jun.2002			4	Adequate		
	18.Dec.1997			4	Adequate		
	06.Jun.2002			4	Adequate		
	29.Mar.2001			4	Adequate		
	12.Sep.2002			4	Adequate		
	11.Oct.2002			4	Adequate		
	1.Oct.2002			4	Adequate		
Type IV							
	13.Feb.2002			4	Adequate	Part of this review	
	13.Feb.2002						
	27.Dec.2000						

¹ Action codes for DMF Table:

1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type I DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

6 - DMF not available

7 - Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION #	DESCRIPTION
ANDA	75-961	Metformin HCl Tablets (approved January 25, 2002)
IND	55,962	Metformin extended-release tablets (Aura Laboratories, Inc., a subsidiary of Andrx Corporation)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	29-JAN-2003	Office of Compliance
Biopharm	Dissolution Specification.	Pending	
ODS/DMETS LNC	Tradename FORTAMET™ was not recommended, however, DMETS has no objection to the use of the proprietary name Fortamet™		Thomas G. Phillips, RPh HFD-400
Methods Validation	DP Assay and Related Substances determinations HPLC analytical methods will be sent to Agency laboratories for revalidation		
EA	Categorical exclusion	Part of this review	
Microbiology	N/A		

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Executive Summary Section

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA can be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no CMC Phase IV Commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug substance

Metformin, the active component, is an antihyperglycemic agent that belongs to the biguanide class. Their mode of action is well understood, biguanides act primarily by decreasing endogenous hepatic output of glucose by inhibition of gluconeogenesis. Structurally metformin, CN1C=NC2=C1N=CN2, is a low molecular biguanide (129.17 g/mol) synthesized.

Metformin hydrochloride is a white to off-white crystalline compound. The pKa of metformin is 12.4. Metformin is a class 3 (high solubility-low permeability) BCS drug. Metformin hydrochloride, drug substance, is very stable compound with a well characterized stability degradation pathway. Particle size is part of the specifications, and there is no evidence of polymorphism. Approved drug products using metformin hydrochloride as drug substance include immediate release (innovator and generics) formulations, an extended release formulation (Glucophage® XR), and recently in combination drug products, either with sulfonylureas such as Glyburide and Glipizide (Glucovance™ and Metaglip™ tablets, respectively) or with the thiazolidinedione Rosiglitazone (Avandamet™ tablets). Metformin HCl drug substance, used by the applicant Andrx Pharmaceuticals for the manufacture of the drug product Fortamet™ tablets, is manufactured and supplied by (DMF).

Drug Product

The drug product, Fortamet™ 500- and 1000-mg Tablets, is an extended release formulation of metformin hydrochloride designed for once a day administration of metformin. The tablet formulation was developed to provide an **extended release** of the active ingredient using the Andrx's proprietary single composition osmotic tablet (SCOT™) technology. The tablet consists of an **osmotically active core** formulation, which is surrounded by a **semipermeable membrane** and a film coating. Two laser drilled exit ports exist in the membrane, one on either side of the tablet. The osmotically active core contains the drug substance Metformin HCl, and the excipients.

The semipermeable membrane is permeable to water but not to higher molecular weight components. Upon ingestion, water is taken up through the membrane (osmosis), which in turn dissolves the drug and excipients in the core formulation. The dissolved drug and excipients exit through the laser drilled ports in the membrane. The **rate of drug delivery is constant** and dependent upon the maintenance of a constant osmotic gradient across the membrane a situation that exists **as long as there is undissolved drug present in the core tablet**. For Fortamet tablet this occurs when about 1/3 of the drug is released. **Following dissolution of the core components**, the **rate of drug delivery slowly decreases** until the osmotic gradient across the membrane falls to zero at which time delivery ceases. The semipermeable membrane remains basically intact.

during the transit of the dosage form through the gastrointestinal tract and is excreted in the feces. The Andrx's SCOT delivery technology operates in a very similar way to Alza's OROS® oral osmotic delivery technology (single composition versus push-pull™ system, respectively).



Executive Summary Section

The manufacture of the osmotically active core (or inner core) is similar to that of conventional immediate release tablets. However, to obtain the desired extended release tablets, the seal-coated inner cores are additionally coated with the sustained release (SR) coating solution, and subsequently laser drilled, color coated, imprinted and packaged. All of these are within defined in-process control stipulations. Fortamet™ specifications are very similar to those for Bristol Mayer Squibb's approved Glucophage® XR (Metformin HCl extended release tablets). Biconvex-shaped, white round 500- and 1000-mg tablets are distinguished by size and debossing.

Fortamet™ Tablets are packaged in bottles and in blister packages. The drug product stability has been evaluated in containers of 30-, 60-, 100- and 1000-count HDPE bottles as well as unit dose blister packages. It is available to patients in 60 cc (500-mg strength) and 100 cc (1000-mg strength) white high-density polyethylene bottles containing 60 tablets, secured with child resistant white caps. Larger capacity HDPE bottles of 1000-counts are also commercially available to Pharmacies and Health Care Centers. The results of the stability studies show the drug product compatibility with the packaging materials and reconfirm the expected stability of metformin hydrochloride in solid oral dosage forms. Consistent with the results of the stability study, an expiration period of 24 months has been granted for Fortamet™ tablets packaged in bottles and 12 months in blister packages, at the recommended storage condition (USP controlled room temperature). Based on the observed degradation trends it is expected that Fortamet™ tablets will remain within specifications for a significant longer period of time. Those expiration dates were limited by the available provided stability data and could be extended with additional supportive data from the ongoing stability study.

Currently, Glucophage® XR a Metformin hydrochloride extended release drug product is available in the market. At the time of Andrx submission of this NDA, Bristol-Myers Squibb Pharmaceutical's Glucophage® XR, which was approved on October 2000, was available only in 500-mg tablets.

The Agency considerations for accepting other Metformin HCl extended release formulation were mainly clinically based. Andrx's Fortamet™ claimed clinical benefits included: (1) clinical studies up to 2500-mg/day (PI Glucophage® XR states "... the maximum recommended daily dose of Glucophage® XR is 2000 mg."), (2) Patient compliance, if a patient is prescribed 2000 mg/daily, this would require two Fortamet tablets instead of four Glucophage® XR tablets (patient compliance decreases relative to the number of daily doses and number of pills), (3) Patient convenience, the 500-mg tablet of Fortamet™ is significantly smaller than the same dosage of Glucophage® XR, advantageous to patients who have difficulty swallowing (e.g., dysphagia caused by diabetic neuropathy) and (4) Effects on triglycerides appear to be less pronounced than those occurring with Glucophage® XR (although no claim is sought by Andrx).

B. Description of How the Drug Product is Intended to be Used

Fortamet™ Tablets is intended to be used orally as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes mellitus whose hyperglycemia cannot be satisfactorily managed with diet and exercise. The drug product can be used either as monotherapy or in combination with a sulfonylurea or insulin. Dosage is based on effectiveness and tolerability, and should not exceed the maximum recommended daily dose of 2500 mg once daily with the evening meal. The usual starting dose is 1000-mg once daily, although 500-mg may be utilized when clinically appropriate. Dosages increases should be made in increments of 500-mg weekly (to reduce gastrointestinal side effects and to permit identification of the minimum dose required), up to a maximum of 2500-mg once daily with the evening meal. As any other metformin containing drug product, in the warning section of the package insert there is a black box cautioning for potential complications due to development of lactic acidosis. Lactic acidosis -characterized by elevated blood lactate levels (> 5 mmol/L), decreased blood pH, electrolyte unbalance with an increased anion gap- is a rare, but serious (fatal in 50 % of the cases) metabolic complication that can occur due to metformin accumulation (plasma levels > 5 µg/mL) during treatment with the drug product. Fortamet™ tablets should be stored at controlled room temperature. Excessive heat and humidity should be avoided.



CHEMISTRY REVIEW



Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The minor CMC deficiencies, acceptable BSE-free certificate or BSE risk statement for magnesium stearate and acceptable packaging labeling, have been adequately addressed by the applicant. All manufacturing facilities are acceptable. Based on the information provided in the submission this application **can be approved** from the Chemistry, Manufacturing and Controls (CMC) standpoint.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review	Xavier Ysern
ChemistryTeamLeaderName/Date	Stephen Moore
ProjectManagerName/Date	Jena Weber

C. CC Block

2 Page(s) Withheld



 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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this page is the manifestation of the electronic signature.**

/s/

Xavier Ysern
8/1/03 02:13:29 PM
CHEMIST

Stephen Moore
8/1/03 02:50:56 PM
CHEMIST



NDA 21-574

Fortamet™ Extended-Release Tablets

Metformin HCl, USP ER Tablets

**Andrx Labs, Inc.
(Andrx)**

**Xavier Ysern, PhD
HFD-510**



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 C. CC Block 8

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CHEMISTRY REVIEW



Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-574
2. REVIEW # 1
3. REVIEW DATE: 12-MAY-2003
4. REVIEWER: Xavier Ysem
5. PREVIOUS DOCUMENTS: Document(s) Document Date
-- --
6. SUBMISSION(S) BEING REVIEWED: Submission(s) Reviewed Document Date
Original 17-DEC-2002
Amendment 29-JAN-2003
7. NAME & ADDRESS OF APPLICANT:
Name: Andrx Labs, Inc. phone (201) 883-1898
Address: 401 Hackensack Avenue
Hackensack, NJ 07601
Representative: Nicholas J. Farina, Vice President Regulatory Affairs
Telephone: (610) 428-2417 Fax: (201) 883-1893
8. DRUG PRODUCT NAME/CODE/TYPE:
a) Proprietary Name: Fortamet™ ER Tablets
b) Non-Proprietary Name (USAN): Metformin HCl Extended-Release Tablets
c) Code Name: --
d) Chem. Type/Submission Priority:
▪ Chem. Type: Type 4
▪ Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: --
10. PHARMACOLOGICAL CATEGORY: Proposed for the treatment of Type 2 diabetes mellitus as an adjunct to diet and exercise
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 500-mg and 1000-mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]: Not a SPOTS product



CHEMISTRY REVIEW



Chemistry Review Data Sheet

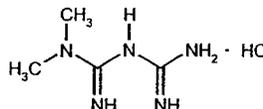
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WEIGHT:

Metformin Hydrochloride

$C_4H_{11}N_5 \cdot HCl$

MW = 129.17 + 36.46 = 165.63

CAS 657-25-9 (free base) 1115-70-4 (hydrochloride)



N,N-Dimethylimidodicarbonimidic diamine monohydrochloride or *N,N*-Dimethylbiguanide HCl

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	LOA date	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
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Type III							
	16.Mar.2001			4	Adequate		
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	06.Aug.2002			4	Adequate		
	01.Mar.1999			4	Adequate		
	20.Dec.2001			3	Adequate	01-APR-1999	
	03.May.2000			4	Adequate		
	25.May.2001			4	Adequate		
	02.May.2002			4	Adequate		
	07.Jun.2002			4	Adequate		
	18.Dec.1997			4	Adequate		
	06.Jun.2002			4	Adequate		
	29.Mar.2001			4	Adequate		
	12.Sep.2002			4	Adequate		
	11.Oct.2002			4	Adequate		
	11.Oct.2002			4	Adequate		
Type IV							
	13.Feb.2002			4	Adequate	Part of this review	
	13.Feb.2002						
	27.Dec.2000						

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type I DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION #	DESCRIPTION
ANDA	75-961	Metformin HCl Tablets (approved January 25, 2002)
IND	55,962	Metformin extended-release tablets (Aura Laboratories, Inc., a subsidiary of Andrx Corporation)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	29-JAN-2003	Office of Compliance
Biopharm	Dissolution Specification.	Pending	
ODS/DMETS LNC	Tradename FORTAMET™ was not recommended, however, DMETS has no objection to the use of the proprietary name Fortamet™		Thomas G. Phillips, RPh HFD-400
Methods Validation	DP Assay and Related Substances determinations HPLC analytical methods will be sent to Agency laboratories for revalidation		
EA	Categorical exclusion	Part of this review	
Microbiology	N/A		

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Executive Summary Section

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is can be approved pending acceptable BSE-free certificate or BSE risk statement for the excipient magnesium stearate, and acceptable carton and immediate container labels for all dosage forms. The requested expiration period of 24 months is granted for dosage forms packaged in HDPE bottles. However, due to the limited stability data provided on blister packaging, a 12 month expiration period is granted for the blister presentations.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no CMC Phase IV Commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug substance

Metformin, the active component, is an antihyperglycemic agent that belongs to the biguanide class. Their mode of action is well understood, biguanides act primarily by decreasing endogenous hepatic output of glucose by inhibition of gluconeogenesis. Structurally metformin, [] is a low molecular biguanide (129.17 g/mol) synthesized [] It is synthesized [] Metformin hydrochloride is a white to off-white crystalline compound. The pKa of metformin is 12.4. Metformin is a class 3 (high solubility-low permeability) BCS drug. Metformin hydrochloride, drug substance, is very stable compound with a well characterized stability degradation pathway. Particle size is part of the specifications, and there is no evidence of polymorphism. Approved drug products using metformin hydrochloride as drug substance include immediate release (innovator and generics) formulations, an extended release formulation (Glucophage® XR), and recently in combination drug products, either with sulfonylureas such as Glyburide and Glipizide (Glucovance™ and Metaglip™ tablets, respectively) or with the thiazolidinedione Rosiglitazone (Avandamet™ tablets). Metformin HCl drug substance, used by the applicant Andrx Pharmaceuticals for the manufacture of the drug product Fortamet™ tablets, is manufactured and supplied by [] (DMF [])

Drug Product

The drug product, Fortamet™ 500- and 1000-mg Tablets, is an extended release formulation of metformin hydrochloride designed for once a day administration of metformin. The tablet formulation was developed to provide an extended release of the active ingredient using the Andrx's proprietary single composition osmotic tablet (SCOT™) technology. The tablet consists of an osmotically active core formulation, which is surrounded by a semipermeable membrane and a film coating [] Two laser drilled exit ports exist in the membrane, one on either side of the tablet. The osmotically active core contains the drug substance Metformin HCl, and the [] excipients [] The semipermeable membrane [] is permeable to water but not to higher molecular weight components. Upon ingestion, water is taken up through the membrane (osmosis), which in turn dissolves the drug and excipients in the core formulation. The dissolved drug and excipients exit through the laser drilled ports in the membrane. The rate of drug delivery is constant and dependent upon the maintenance of a constant osmotic gradient across the membrane a situation that exists as long as there is undissolved drug present in the core tablet. For Fortamet tablet this occurs when about [] of the drug is released. Following dissolution of the core components, the rate of drug delivery slowly decreases until the osmotic gradient across the membrane falls to zero at which time delivery



Executive Summary Section

ceases. The semipermeable membrane remains basically intact [

] during the transit of the dosage form through the gastrointestinal tract and is excreted in the feces. The Andrx's SCOT delivery technology operates in a very similar way to Alza's OROS® oral osmotic delivery technology (single composition versus push-pull™ system, respectively).

The manufacture of the osmotically active core (or inner core) is similar to that of conventional immediate release tablets [However, to obtain the desired extended release tablets, the seal-coated inner cores are additionally coated with the sustained release (SR) coating solution, and subsequently laser drilled, color coated, imprinted and packaged. All of these are within defined in-process control stipulations. Fortamet™ specifications are very similar to those for Bristol Mayer Squibb's approved Glucophage® XR (Metformin HCl extended release tablets). Biconvex-shaped, white round 500- and 1000-mg tables are distinguished by size and debossing.

Fortamet™ Tablets are packaged in bottles and in blister packages. The drug product stability has been evaluated in containers of 30-, 60-, 100- and 1000-count HDPE bottles as well as unit dose blister packages. It is available to patients in 60 cc (500-mg strength) and [] (1000-mg strength) white high-density polyethylene bottles containing 60 tablets, secured with child resistant white [] caps. Larger capacity HDPE bottles of 1000-counts are also commercially available to Pharmacies and Health Care Centers. The results of the stability studies show the drug product compatibility with the packaging materials and reconfirm the expected stability of metformin hydrochloride in solid oral dosage forms. Consistent with the results of the stability study, an expiration period of 24 months has been granted for Fortamet™ tablets packaged in bottles and 12 months in blister packages, at the recommended storage condition (USP controlled room temperature). Based on the observed degradation trends it is expected that Fortamet™ tablets will remain within specifications for a significant longer period of time. Those expiration dates were limited by the available provided stability data and could be extended with additional supportive data from the ongoing stability study.

Currently, Glucophage® XR a Metformin hydrochloride extended release drug product is available in the market. At the time of Andrx submission of this NDA, Bristol-Myers Squibb Pharmaceutical's Glucophage® XR, which was approved on October 2000, was available only in 500-mg tablets [

] The Agency considerations for accepting other Metformin HCl extended release formulation were mainly clinically based. Andrx's Fortamet™ claimed clinical benefits included: (1) clinical studies up to 2500-mg/day (PI Glucophage® XR states "... the maximum recommended daily dose of Glucophage® XR is 2000 mg."), (2) Patient compliance, if a patient is prescribed 2000 mg/daily, this would require two Fortamet tablets instead of four Glucophage® XR tablets (patient compliance decreases relative to the number of daily doses and number of pills), (3) Patient convenience, the 500-mg tablet of Fortamet™ is significantly smaller than the same dosage of Glucophage® XR, advantageous to patients who have difficulty swallowing (e.g., dysphagia caused by diabetic neuropathy) and (4) Effects on triglycerides appear to be less pronounced than those occurring with Glucophage® XR (although no claim is sought by Andrx).

B. Description of How the Drug Product is Intended to be Used

Fortamet™ Tablets is intended to be used orally as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes mellitus whose hyperglycemia cannot be satisfactorily managed with diet and exercise. The drug product can be used either as monotherapy or in combination with a sulfonylurea or insulin. Dosage is based on effectiveness and tolerability, and should not exceed the maximum recommended daily dose of 2500 mg once daily with the evening meal. The usual starting dose is 1000-mg once daily, although 500-mg may be utilized when clinically appropriate. Dosages increases should be made in increments of 500-mg weekly (to reduce gastrointestinal side effects and to permit identification of the minimum dose required), up to a maximum of 2500-mg once daily with the evening meal. As any other metformin containing drug product, in the warning section of the package insert there is a black box cautioning for potential complications due to development of lactic acidosis. Lactic acidosis -characterized by elevated blood lactate levels (> 5 mmol/L), decreased blood pH, electrolyte unbalance with an increased anion gap- is a rare, but serious (fatal in 50 % of the cases) metabolic complication that



Executive Summary Section

can occur due to metformin accumulation (plasma levels > 5 µg/mL) during treatment with the drug product. Fortamet™ tablets should be stored at controlled room temperature. Excessive heat and humidity should be avoided.

C. Basis for Approvability or Not-Approval Recommendation

There are minor CMC deficiencies. All manufacturing facilities are acceptable. Based on the information provided in the submission this application **can be approved** from the Chemistry, Manufacturing and Controls (CMC) standpoint, **pending** acceptable BSE-free certificate or BSE risk statement for magnesium stearate, and acceptable packaging labeling is provided.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review	Xavier Ysern
ChemistryTeamLeaderName/Date	Stephen Moore
ProjectManagerName/Date	Jena Weber

C. CC Block

34 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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this page is the manifestation of the electronic signature.**

/s/

Xavier Ysern
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CHEMIST

Stephen Moore
6/23/03 05:27:45 PM
CHEMIST