

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-026

CHEMISTRY REVIEW(S)

NDA 22-026

Amlodipine Besylate Orally Disintegrating Tablets

Synthon Pharmaceuticals Inc.

Martin Haber, Ph.D.
Division of Pre-Marketing Assessment/ONDQA

Review for
Division of Cardio-Renal Drug Products



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Chemistry Review Data Sheet

1. NDA 22-026
2. REVIEW #2
3. REVIEW DATE: November 29, 2006
4. REVIEWER: Martin Haber, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA	1/31/06
Amendment	6/8/06
Chemistry Review #1	9/21/06
CMC IR Letter	9/27/06

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	10/17/06

7. NAME & ADDRESS OF APPLICANT:

Name: Synthon Pharmaceuticals, Inc.
 Address: 9000 Development Drive, P.O. Box 110487,
 Research Triangle Park, NC 27709
 Representative: Michael H. Hinckle, VP and General Counsel
 Telephone: 919-536-1304

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Not yet proposed
- b) Non-Proprietary Name (USAN): Amlodipine Besylate
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3, New Formulation
 - Submission Priority: S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), reference drug Norvasc (amlodipine besylate) Tablets, NDA 19-727, approved in 1992

10. PHARMACOL. CATEGORY: Calcium channel blocker for treatment of hypertension

11. DOSAGE FORM: Orally Disintegrating Tablets

12. STRENGTH/POTENCY: 2.5, 5 and 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: x Rx OTC

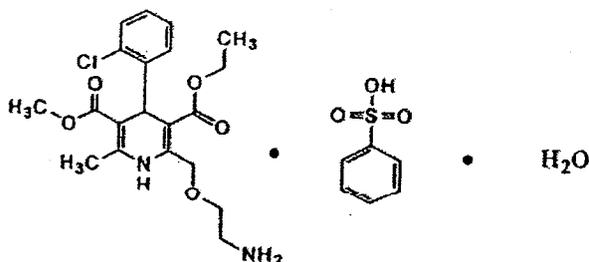
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed

 X Not a SPOTS product

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

3-ethyl-5-methyl-(±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate monohydrate

Structural Formula:



Molecular Formula:

C₂₀H₂₅ClN₂O₅·C₆H₅SO₃·H₂O

Molecular Weight:

585.07 g/mol

17. RELATED/SUPPORTING DOCUMENTS:



Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
18872	II	Synthon BV	Amlodipine Besylate Monohydrate, Drug Substance	1	Adequate	11/29/06	Reviewed by this reviewer
	IV			3	Adequate	8/30/05	reviewed by Dr. S. Ding
	III			4	N/A		Review not required for compendial excipient
	III			3	Adequate	9/21/03	reviewed by Dr. J. Boal
	IV			3	Adequate	9/2/03	reviewed by Dr. B. Wu
	III			3	Adequate	9/5/01	Reviewed by Dr. R. Frankewich
	III			3	Adequate	9/15/03	Reviewed by Dr. J. Salemm
	III			3	Adequate	7/23/04	Reviewed by Dr. C. Bertha
	III			4	N/A		Review not required, certified for food use

b(4)

¹ Action codes for DMF Table:

1 - DMF Reviewed.

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

2 - Type 1 DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted



Chemistry Review Data Sheet

- 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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending		
Pharm/Tox	NA		
Biopharm	NA		
Methods Validation	NA		
DMETS	NA		
EA	NA		
Microbiology	NA		



The Chemistry Review for NDA 22-026

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval, pending a satisfactory facility inspection report.

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

NA

II. Summary of Chemistry Assessments

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

The drug product is an orally disintegrating tablet. No tradename has been proposed. There are three proposed strengths, equivalent to 2.5, 5 and 10 mg of amlodipine, with tablet weights of 70, 140 and 280 mg and colors white, yellow and pink, respectively. In addition to the active ingredient, the round, biconvex tablets contain _____ hydroxypropyl cellulose, _____ microcrystalline cellulose, mint menthol _____ Sucralose, iron oxide red and yellow color, and magnesium stearate. The drug product tablets are manufactured by Rottendorf Pharma GmbH, Germany and tested by Synthron BV, The Netherlands. The critical process steps are _____ and _____

b(4)

Specifications include _____

_____ was added to the specifications at the request of the Agency. Based on the batch data, the acceptance limit for total impurities was tightened. The drug product is packaged in _____ white, opaque, 75 mL round bottles containing either 14 or 30 tablets with a 45 mm white child resistant closure. Stability data for twelve months was submitted. No significant changes were observed over this period. This adequately supports the proposed expiration dating period of 24 months at 25°C.

b(4)

The original NDA was reviewed on 9/21/06. CMC comments were sent to the applicant on 9/27/06, and the applicant's complete response was made in the 10/17/06 Amendment which was reviewed herein and found satisfactory.

The drug substance is amlodipine besylate monohydrate. It is a calcium channel blocker of the dihydropyridine class, made by : _____ Amlodipine contains one chiral center but is made as the _____ Specifications include : _____

b(4)

_____ The drug substance is stable at _____

Executive Summary Section

room temperature. The drug substance is manufactured by Synthron Argentina S.A. using the process described in Drug Master File #18872. The DMF holder is Synthron BV, who is also the drug product release tester, and the US Agent is Synthron Pharmaceuticals Inc., the NDA applicant.

The original DMF was reviewed on 7/31/06 and found inadequate. Major deficiencies related to characterization, synthesis and testing. Comments were sent on 8/3/06 to the US Agent for the DMF, who in this case is also the NDA applicant. The DMF was amended and DMF 18872 was found adequate in DMF Review #2 dated 11/29/06.

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

The drug product is indicated for the treatment of angina. Instead of an immediate release tablet formulation as in the reference drug, for this NDA an orally disintegrating tablet formulation is proposed to be marketed. The proposed strengths are 2.5, 5, and 10 mg of amlodipine. The usual initial oral dose is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly individuals, or patients with hepatic insufficiency may be started on 2.5 mg once daily. Standard oral dose packaging is used (— bottle and cap). The expiry period is two years when stored at room temperature.

b(4)

C. Basis for Approvability or Not-Approval Recommendation

The chemistry, manufacturing, and control information provided is satisfactory. The drug substance DMF is adequate for this application. Facility inspection results are pending.

III. Administrative**A. Reviewer's Signature**

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

4 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Martin Haber
11/29/2006 02:01:36 PM
CHEMIST

Ramesh Sood
11/29/2006 02:20:21 PM
CHEMIST

NDA 22-026

Amlodipine Besylate Orally Disintegrating Tablets

Synthon Pharmaceuticals Inc.

Martin Haber, Ph.D.

Division of Pre-Marketing Assessment/ONDQA

Review for

Division of Cardio-Renal Drug Products



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 A. Labeling & Package Insert.....35

 B. Environmental Assessment Or Claim Of Categorical Exclusion.....35

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Chemistry Review Data Sheet

1. NDA 22-026
2. REVIEW #1
3. REVIEW DATE: September 27, 2006
4. REVIEWER: Martin Haber, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NA	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	1/31/06
Amendment	6/8/06

7. NAME & ADDRESS OF APPLICANT:

Name:	Synthon Pharmaceuticals, Inc.
Address:	9000 Development Drive, P.O. Box 110487, Research Triangle Park, NC 27709
Representative:	Michael H. Hinckle, VP and General Counsel
Telephone:	919-536-1304

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Not yet proposed
- b) Non-Proprietary Name (USAN): Amlodipine Besylate
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):

Chemistry Review Data Sheet

- Chem. Type: 3, New Formulation
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), reference drug Norvasc (amlodipine besylate) Tablets, NDA 19-727, approved in 1992

10. PHARMACOL. CATEGORY: Calcium channel blocker for treatment of hypertension

11. DOSAGE FORM: Orally Disintegrating Tablets

12. STRENGTH/POTENCY: 2.5, 5 and 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

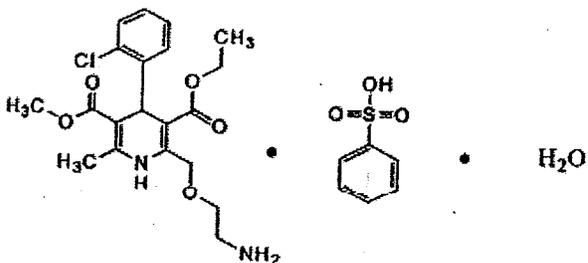
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed

Not a SPOTS product

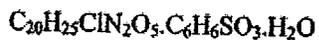
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3-ethyl-5-methyl-(±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate monohydrate

Structural Formula:



Molecular Formula:



Molecular Weight:

585.07 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
18872	II	Synthon BV	Amlodipine Besylate Monohydrate, Drug Substance	1	Inadequate	July 31, 2006	Reviewed by this reviewer
	IV			3	Adequate	8/30/05	reviewed by Dr. S. Ding
	III			4	N/A		Review not required for compendial excipient
	III			3	Adequate	9/21/03	reviewed by Dr. J. Boal
	IV			3	Adequate	9/2/03	reviewed by Dr. B. Wu
	III			3	Adequate	9/5/01	Reviewed by Dr. R. Frankewich
	III			3	Adequate	9/15/03	Reviewed by Dr. J. Salemme
	III			3	Adequate	7/23/04	Reviewed by Dr. C. Bertha
	III			4	N/A		Review not required, certified for food use

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 –Type 1 DMF

Chemistry Review Data Sheet

- 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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending		
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	NA		
DMETS	Pending		
EA	NA		
Microbiology	NA		

The Chemistry Review for NDA 22-026

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable, pending resolution of chemistry deficiencies and satisfactory facility inspections. Comments were sent to the applicant on 9/27/06, see final page of review.

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

NA

II. Summary of Chemistry Assessments

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

The drug product is an orally disintegrating tablet. No tradename has been proposed. There are three proposed strengths, equivalent to 2.5, 5 and 10 mg of amlodipine. In addition to the active ingredient, the tablets contain _____ hydroxypropyl cellulose, _____ microcrystalline cellulose, mint menthol _____ Sucralose, iron oxide red and yellow color, and magnesium stearate. The drug product tablets are manufactured by Rottendorf Pharma GmbH, Germany and tested by Synthron BV, The Netherlands. The critical process steps are _____ and _____ Specifications include _____

b(4)

b(4)

_____ was added to the specifications at the request of the Agency. Based on the batch data, the acceptance limit for total impurities should be tightened. The drug product is packaged in _____ white, opaque, 75 mL round bottles containing either 14 or 30 tablets with a 45 mm white child resistant closure. Stability data for only six months was submitted. No significant trends were observed over this short period. Updated stability data will be required to support the proposed expiration dating period of 24 months at 25°C.

b(4)

The drug substance is amlodipine besylate monohydrate. It is a calcium channel blocker of the dihydropyridine class, made by _____ Amlodipine contains one chiral center but is made as the _____ Specifications include _____

b(4)

_____ The drug substance is manufactured by Synthron Argentina S.A. using the process described in Drug Master File #18872. The DMF holder is Synthron BV, who is also the drug product release tester. The DMF was reviewed on 7/31/06 and found inadequate. Major deficiencies relate to characterization, synthesis and testing. Comments were sent on 8/3/06 to the US Agent for the DMF, who in this case is also the NDA applicant.

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

The drug product is indicated for the treatment of angina. Instead of an immediate release tablet formulation as in the reference drug, for this NDA an orally disintegrating tablet formulation is proposed to be marketed. The proposed strengths are 2.5, 5, and 10 mg of amlodipine. The usual initial oral dose is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly individuals, or patients with hepatic insufficiency may be started on 2.5 mg once daily. Standard oral dose packaging is used (— bottle and cap). The applicant is requesting an expiry of two years when stored at room temperature. Additional stability data to support this request is required.

b(4)

C. Basis for Approvability or Not-Approval Recommendation

The chemistry, manufacturing, and control information provided is not adequate. The application is deficient for the drug substance DMF, drug product specifications, and insufficient stability data. Facility inspection results are pending.

III. Administrative

A. Reviewer's Signature

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

28 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Martin Haber
9/28/2006 11:47:50 AM
CHEMIST

Ramesh Sood
9/28/2006 01:10:46 PM
CHEMIST

Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I

OND Division: Division of Cardio-Renal Products
NDA: 22-026
Applicant: Synthron
Stamp Date: 1-Feb-2006
PDUFA Date: 1-Dec-2006
Trademark: Not proposed
Established Name: Amlodipine besylate [USAN]
Dosage Form: Orally Disintegrating Tablet, 2.5, 5, and 10 mg
Route of Administration: Oral
Indication: Treatment of angina and hypertension

PAL: Kasturi Srinivasachar, Ph.D.

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Summary and Critical Issues:

Summary

Background

This is a 505(b)(2) application. Synthron has developed an orally disintegrating tablet formulation of the amlodipine besylate active ingredient that is currently marketed by Pfizer Inc. under the trade name Norvasc tablets (approved NDA 19-787). Based on patent information available in the Orange Book, Synthron requests approval of its NDA no earlier than September 25, 2007. Synthron is proposing to support approval of its NDA with a combination of the published literature on amlodipine besylate, FDA's previous findings of safety and efficacy of Navasc Tablets, and data from comparative bioavailability studies of the two 10 mg strength formulations.

Drug Substance

Amlodipine is a calcium ion influx inhibitor (slow channel-blocker or calcium ion antagonist) and inhibits influx of calcium into cardiac and smooth muscle. The antihypertensive action of amlodipine is due to a relaxant effect on vascular smooth muscle. The mechanism by which angina is relieved is not fully determined but may involve reduction of the total peripheral resistance (afterload) and dilation of the main coronary arteries and arterioles. The active ingredient is amlodipine besylate monohydrate.

Drug Substance Microbiology Testing:

b(4)

Note: This site is also listed for microbiology testing of the drug product. However, neither the drug substance nor drug product specifications include any microbiology testing.

EES has been submitted for all sites by Dr. Scott Goldie, PM.

A table of specifications was provided with the NDA, see attachment:

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

Table 7: Composition per Tablet of Each Strength of Amlodipine besylate 2.5 mg, 5 mg, and 10 mg Orally Disintegrating Tablets

Ingredient	2.5 mg Tablet	5 mg Tablet	10 mg Tablet
Amlodipine besylate monohydrate ¹	70.00	140.00	280.00
hydroxypropyl cellulose			
microcrystalline cellulose			
Mint menthol ²			
Sucralose			
Iron oxide yellow			
Iron oxide red			
Magnesium stearate			
Total	70.00	140.00	280.00

b(4)

¹ Calculated as Amlodipine besylate monohydrate.
² Mint menthol

The drug product is produced by a contract manufacturer. The final release of drug product is performed at Synthron Pharmaceuticals, Inc., RTC, NC (NDA sponsor).

Site of manufacturing, packaging, labeling and limited testing:
 Rottendorf Pharma GmbH
 Ostenfelder Str. 51-61
 59320 Ennigerloh
 Germany

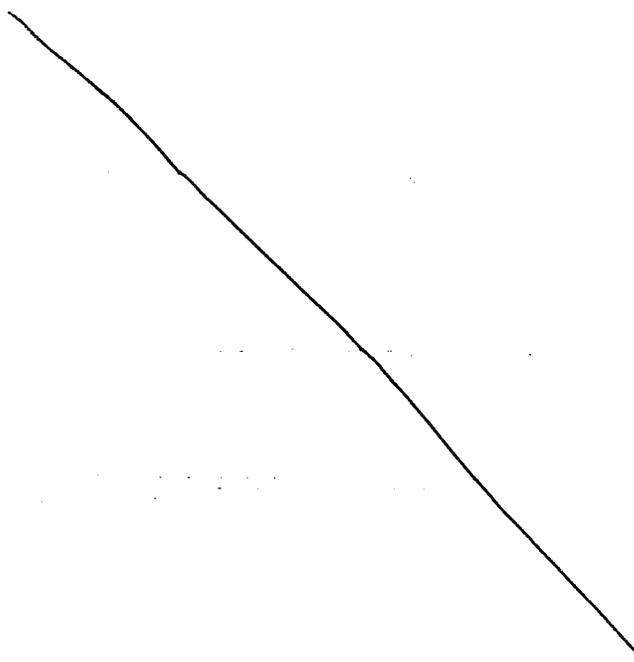
Finished product release and stability test site:
 Synthron BV
 Microweg 22
 PO Box 7071
 6503 GN Nijmegen
 The Netherlands

Note: This firm is also the Drug Substance DMF Holder.

EES has been submitted for the sites.

Release and stability specifications for the drug product have been provided, specifications are essentially identical for all three strengths on a percent basis, see attachment:

Table 9: Specifications for Release Testing of Amlodipine besylate 2.5 mg Orally Disintegrating Tablets

Parameter	Specification
Appearance	White, round, biconvex tablets. The tablets are debossed with "ADP 2.5" on one side and "ODT" on the other side.
	

b(4)

Note: The stability acceptance limits for assay are wider, _____ but otherwise identical.

b(4)

The specifications appear too broad and probably could be tightened significantly. This is a review issue. There is no disintegration specification.

There are two packaging configurations:

- a. _____, white, 75 mL round bottle with 45 mm twist-off child resistant closure containing 14 or 30 tablets

b(4)

Primary Stability data:

3 commercial scale batches of each strength packaged in _____ bottles:

- 25°C/60% RH (0, 3, 6 months)
- 30°C/60% RH (0, 3, 6 months)
- 40°C/75% RH (0, 3, 6 months)
- Photostability Direct exposure in open dish (200 Wh/m², 1.2 Mlux.h)

NDA FILEABILITY CHECKLIST

NDA Number: 22-026 **Applicant:** Synthron Pharmaceuticals, Inc. **Stamp Date:** 2/1/06

Drug Name: Amlodipine Besylate Orally Disintegrating Tablets (ODT)

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) YES

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	x		CTD format, 16 volume paper submission, 60 page Quality Overall Summary
2	Is the section indexed and paginated adequately?	x		
3	On its face, is the section legible?	x		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	x		EES entered by S. Goldie, see below
5	Is a statement provided that all facilities are ready for GMP inspection?	x		
6	Has an environmental assessment report or categorical exclusion been provided?	x		Categorical exclusion requested.
7	Does the section contain controls for the drug substance?	x		Type II, DMF# 18872 referenced for drug substance, DMF IS NOW IN ACTIVE STATUS
8	Does the section contain controls for the drug product?	x		
9	Has stability data and analysis been provided to support the requested expiration date?		x	Requested 24 month expiry, but provided only 6 months data.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		IND 72,363 file contains pre-NDA meeting notes.
11	Have draft container labels been provided?	x		Vol. 1
12	Has the draft package insert been provided?	x		Vol. 1
13	Has an investigational formulations section been provided?	x		A single bioequivalence study using 10 mg ODT's was done
14	Is there a Methods Validation package?	x		
15	Is a separate microbiological section included?		x	This is not needed because the dosage form is a tablet.

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Review Chemist: M. Haber, Ph.D.
Branch Chief: Ramesh Sood, Ph.D.

Date: March 20, 2006
Date:

NDA Number: 22-026 Applicant: Synthon Pharmaceuticals Stamp Date: 2/1/06

Have all DMF References been Identified?

DMF Number	Holder	Description	LOA Included	Status
18872	Synthon BV	Amlodipine Besystate Monohydrate, Drug Substance	Yes	DMF is now in Active status and available for review
			Yes	Adequate, reviewed by Dr. S. Ding on 8/30/05
			Yes	Pending review, if necessary
			Yes	Adequate, reviewed by Dr. J. Boal on 9/21/03
			Yes	Adequate, reviewed by Dr. B. Wu on 9/2/03
			Yes	Adequate, reviewed by Dr. R. Frankewich on 9/5/01
			Yes	Adequate, reviewed by Dr. J. Salemme on 9/15/03
			Yes	Adequate, reviewed by Dr. C. Bertha on 7/23/04
			Yes	Review not required, adequate information provided in NDA

b(4)

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/s/

Martin Haber
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Ramesh Sood
4/5/2006 02:50:11 PM
CHEMIST