

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-026

**ADMINISTRATIVE and
CORRESPONDENCE
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

22-026

NAME OF APPLICANT / NDA HOLDER

Synthon Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

None

ACTIVE INGREDIENT(S)

Amlodipine besylate

STRENGTH(S)

2.5mg, 5mg, 10mg

DOSAGE FORM

Oral Disintegrating Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

6,828,339

b. Issue Date of Patent

12/7/2004

c. Expiration Date of Patent

11/20/2022

d. Name of Patent Owner

Synthon IP, Inc.

Address (of Patent Owner)

7130 Heritage Village Plaza, Suite 202

City/State

Gainesville, VA

ZIP Code

20155

FAX Number (if available)

(703) 753-0683

Telephone Number

(703) 753-5256

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

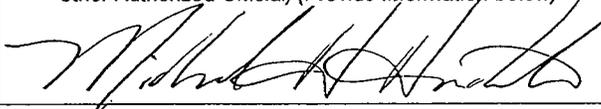
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed
3/20/2006



NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Michael H. Hinckle, Esq.

Address

9000 Development Drive
P.O. Box 110487

City/State

Research Triangle Park, NC

ZIP Code

27709

Telephone Number

(919) 493-6006

FAX Number (if available)

(919) 493-6104

E-Mail Address (if available)

mhinckle@synthon.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahtm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.



Paragraph III Certification
US Patent No. 4,572,909

In accordance with section 505(b)(2)(A) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), Synthon Pharmaceuticals, Inc. ("Synthon") hereby provides its Patent Certification for our New Drug Application for Amlodipine besylate 2.5 mg, 5 mg and 10 mg orally disintegrating tablets. Synthon's NDA is submitted under FDCA § 505(b)(2) and incorporates by reference the FDA's previous finding of safety and efficacy for the Norvasc® drug product described in approved NDA # 19-787.

Synthon hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 4,572,909 held by Pfizer, Inc. will expire on July 31, 2006 but that, for the purposes of this Patent Certification, such expiration date has been extended to January 31, 2007 pursuant to FDCA § 505A. In accordance with FDCA § 505(b)(2)(A)(iii) and 21 C.F.R. § 314.50(i)(1)(i)(3), Synthon is hereby requesting approval of its NDA no earlier than January 31, 2007.

Synthon Pharmaceuticals, Inc.

A handwritten signature in black ink, appearing to read "Michael H. Hinckle", is written over a horizontal line.

Michael H. Hinckle,
VP and General Counsel

1-31-06

Date



**Paragraph III Certification
US Patent No. 4,879,303**

In accordance with section 505(b)(2)(A) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), Synthon Pharmaceuticals, Inc. ("Synthon") hereby provides its Patent Certification for our New Drug Application for Amlodipine besylate 2.5 mg, 5 mg and 10 mg orally disintegrating tablets. Synthon's NDA is submitted under FDCA § 505(b)(2) and incorporates by reference the FDA's previous finding of safety and efficacy for the Norvasc[®] drug product described in approved NDA # 19-787.

Synthon hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 4,879,303 held by Pfizer, Inc. will expire on March 25, 2007 but that, for the purposes of this Patent Certification, such expiration date has been extended to September 25, 2007 pursuant to FDCA § 505A. In accordance with FDCA § 505(b)(2)(A)(iii) and 21 C.F.R. § 314.50(i)(1)(i)(3), Synthon is hereby requesting approval of its NDA no earlier than September 25, 2007.

Synthon Pharmaceuticals, Inc.

A handwritten signature in black ink, appearing to read "Michael H. Hinckle", written over a horizontal line.

Michael H. Hinckle,
VP and General Counsel

1-31-06
Date

EXCLUSIVITY SUMMARY

NDA # 22026

SUPPL #

HFD #

Trade Name None

Generic Name Amlodipine ~~Tablets~~ Orally Disintegrating Tablets

b(4)

Applicant Name Synthron Pharmaceuticals, Inc.

Approval Date, If Known September 28, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The firm conducted a bioequivalence study under fasting conditions comparing the highest proposed strength (10 mg) of amlodipine orally disintegrating tablet to the approved 10-mg NORVASC® tablet reference product manufactured by Pfizer (Study CSP.US01.ADP.odt10.001/ CPA 235-05).

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

NA

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA

#(s).

NDA# 19787

Norvasc 2.5, 5, and 10 mg Tablets

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-364

Lotrel (benazepril HCl/amlodipine besylate)

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====
Name of person completing form: Denise M. Hinton

Title: Regulatory Health Project Manager

Date: September 21, 2007

Name of Office/Division Director signing form: Norman Stockbridge, MD, PhD

Title: Division Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA: 22-026 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: February 1, 2006 PDUFA Goal Date: December 1, 2006

HFD-110 Trade and generic names/dosage form: Amlodipine besylate 2.5, 5, and 10 mg orally disintegrating tablets

Applicant: Synthon Pharmaceuticals, Inc. Therapeutic Class: CCB

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *New formulation

- Yes. Please proceed to the next question.
- No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 3

Indications: 1. hypertension 2. chronic stable angina 3. vasospastic angina

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 22-026

Page 3

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)

Attachment A
(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Denise Hinton

12/1/2006 10:06:38 AM



REQUEST FOR FULL WAIVER FROM REQUIREMENT OF THE PEDIATRIC REQUIREMENT EQUITY ACT

Pursuant to 21 505b (A)(4)(a) of the Federal Food, Drug, and Cosmetic Act ("FDCA") and 21 C.F.R. (c)(2)(i), Synthon Pharmaceuticals, Inc. ("Synthon") hereby requests a "full waiver" of the pediatric assessment requirement of the Pediatric Research Equity Act ("PREA"). The basis for our request is provided below.

I. Hypertension

Norvasc[®] is indicated for the treatment of hypertension in pediatric patients of ages 6-17 years. Amlodipine ODT offers no therapeutic advantage over the currently marketed product. It is not necessary to duplicate studies in this patient population and to expose patients to a drug which has a well characterized safety and efficacy profile. Regarding treatment of younger children (<6 years of age), *The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents*, recommends that definite indication for initiating pharmacologic therapy should be ascertained before a drug is prescribed. This report recommends amlodipine for children 6-17 years of age.¹

Therefore, Synthon is requesting a full waiver of pediatric studies based on the fact that amlodipine has been previously studied in pediatric patients of ages 6 to 17 years, our amlodipine ODT product offers no clinical benefit over the currently marketed product and drug therapy is not recommended for children under the age of 6 years.

II. Chronic Stable Angina and Vasospastic (Prinzmetal's/Variant) Angina

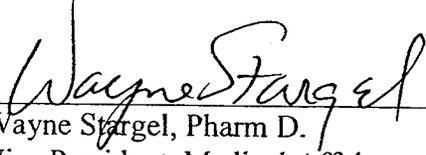
Amlodipine is also indicated for the treatment of chronic stable angina and vasospastic angina (Prinzmetal's or variant angina). The most common cause of angina is arteriosclerosis of the coronary arteries which occurs predominately in adult patients.

Arteriosclerosis is cited in FDA's *Guidance for Industry Recommendations for Complying with the Pediatric Rule (21 CFR 315.55(a) and 601.27(a))* as a disease having an extremely limited applicability to pediatric patients in that the signs and symptoms of this disease occur for the most part in the adult population.²

Therefore, based on this guidance, Synthon is requesting a full waiver of pediatric studies for these indications in subjects under the age of 18 years.

REFERENCES

1. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Bethesda, Maryland: National Heart, Lung, and Blood Institute; 1996
2. Guidance for Industry Recommendations for Complying with the Pediatric Rule (21 CFR 315.55(a) and 601.27(a)). USDHHS, FDA, CDER, and CBER, November 2000.


Wayne Stargel, Pharm D.
Vice President, Medical Affairs

JAN. 31, 2006
Date



Synthon
Argentina S.A.

San Lorenzo, 6th of December of 2005.

GENERIC DRUG ENFORCEMENT ACT OF 1992
DEBARMENT CERTIFICATION STATEMENT

Synthon Argentina S.A. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 (k) of the Federal Food, Drug and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992 under subsection (a) or (b) in connection with this (A)NDA for Amlodipine besylate monohydrate.

Synthon Argentina S.A. certifies further that, during the previous five years, it has not sustained a conviction that is described in subsection (a) or (b) of the Generic Drug Enforcement Act of 1992. In addition, to the best of Synthon Argentina's knowledge, no person affiliated with Synthon Argentina S.A. that was responsible for the development or submission of this application has been convicted of an offense described in (a) or (b) of the Generic Drug Enforcement Act of 1992.



Dr. Andrés Ferrara
Head of QA/QC

6/12/05
Date

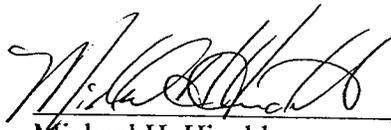


January 31, 2006

GENERIC DRUG ENFORCEMENT ACT OF 1992
DEBARMENT CERTIFICATION STATEMENT

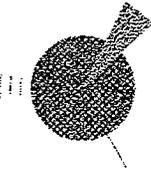
Synthon Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 (k) of the Federal Food, Drug and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992 under subsection (a) or (b) in connection with this NDA for Amlodipine besylate 2.5 mg, 5 mg and 10 mg orally disintegrating tablets.

Synthon Pharmaceuticals, Inc. certifies further that, during the previous five years, it has not sustained a conviction that is described in subsection (a) or (b) of the Generic Drug Enforcement Act of 1992. In addition, to the best of Synthon Pharmaceuticals, Inc.'s knowledge, no person affiliated with Synthon Pharmaceuticals, Inc. that was responsible for the development or submission of this application has been convicted of an offense described in (a) or (b) of the Generic Drug Enforcement Act of 1992.



Michael H. Hinckle
Vice President and General Counsel

1-31-06
Date



September 14, 2005

GENERIC DRUG ENFORCEMENT ACT OF 1992
DEBARMENT CERTIFICATION STATEMENT

Synthon B.V. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 (k) of the Federal Food, Drug and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992 under subsection (a) or (b) in connection with this (A)NDA for Amlodipine Besylate Orally Disintegrating Tablets 2.5 mg, 5 mg and 10 mg.

Synthon B.V. certifies further that, during the previous five years, it has not sustained a conviction that is described in subsection (a) or (b) of the Generic Drug Enforcement Act of 1992. In addition, to the best of Synthon B.V.'s knowledge, no person affiliated with Synthon B.V. that was responsible for the development or submission of this application has been convicted of an offense described in (a) or (b) of the Generic Drug Enforcement Act of 1992.

Drs G. W. Klein Kranenborg
Director QA/Qualified Person Synthon B.V.

September 22, 2005
Date

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____

Name of clinical investigator

Name of

b(4)

_____ is submitted in accordance with 21 CFR part _____

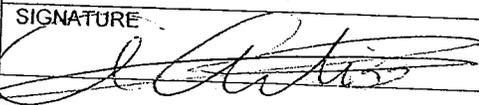
clinical study

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows: NONE (SEE ATTACHED)

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME		TITLE	
Angelo Cornelissen		General Manager	
FIRM / ORGANIZATION			
Synthon Pharmaceuticals, Inc.			
SIGNATURE		DATE	
		3/20/2006	

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

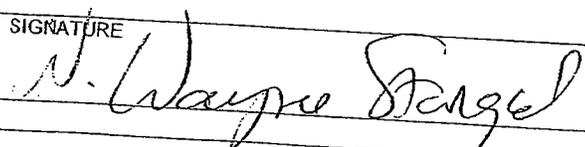
Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list of Clinical Investigators for Study No. CSP.US01.ADP.ODT10.001	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME W. Wayne Stargel, Pharm.D.		TITLE Vice President of Medical Affairs	
FIRM / ORGANIZATION Synthon Pharmaceuticals, Inc.			
SIGNATURE 		DATE July 05, 2005	

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

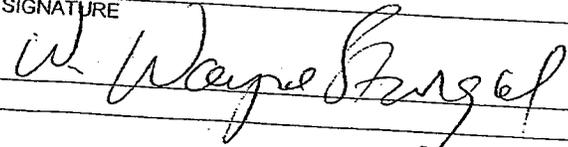
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list of Clinical Investigators for Study No. CSP.US01.ADP.ODT10.002	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME W. Wayne Stargel, Pharm.D.		TITLE Vice President Medical Affairs	
FIRM / ORGANIZATION Synthon Pharmaceuticals, Inc.			
SIGNATURE 			DATE July 05, 2005

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 22-026	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Amlodipine besylate orally disintegrating tablets Established Name: Dosage Form: 2.5 mg, 5 mg, and 10 mg		Applicant: Synthon Pharmaceuticals, Inc.
RPM: Denise M. Hinton		Division: DCRP Phone # (301) 796-1090
<p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>	<p>505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>Norvasc (amlodipine besylate)</p> <p>Provide a brief explanation of how this product is different from the listed drug. Orally disintegrating tablet</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</p> <p><input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date: 27Nov06</p>	
❖ User Fee Goal Date ❖ Action Goal Date (if different)		1Dec06
❖ Actions		
• Proposed action	<input type="checkbox"/> AP <input type="checkbox"/> TA <input checked="" type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR	
• Previous actions (<i>specify type and date for each action taken</i>)	<input checked="" type="checkbox"/> None	
❖ Advertising (<i>approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (<i>indicate dates of reviews</i>)		<input type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics

Review priority: Standard Priority
 Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:

- Fast Track
- Rolling Review
- CMA Pilot 1
- CMA Pilot 2

Orphan drug designation

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)
- Subpart I
- Approval based on animal studies

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)
- Subpart H
- Approval based on animal studies

NDAs and NDA Supplements:

OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)

• Applicant is on the AIP

Yes No

• This application is on the AIP

Yes No

• Exception for review (*file Center Director's memo in Administrative Documents section*)

Yes No

• OC clearance for approval (*file communication in Administrative Documents section*)

Yes Not an AP action

❖ Public communications (approvals only)

• Office of Executive Programs (OEP) liaison has been notified of action

Yes No

• Press Office notified of action

Yes No

• Indicate what types (if any) of information dissemination are anticipated

- None
- FDA Press Release
- FDA Talk Paper
- CDER Q&As
- Other

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
<p>Summary Reviews</p>	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	Dr. Norman Stockbridge 29Nov06
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	NA
<p>Labeling</p>	
❖ Package Insert	
<ul style="list-style-type: none"> Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	None
<ul style="list-style-type: none"> Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	Included
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	Included
❖ Patient Package Insert	
<ul style="list-style-type: none"> Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	None
<ul style="list-style-type: none"> Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	Included
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	Included
❖ Medication Guide	
<ul style="list-style-type: none"> Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	NA
<ul style="list-style-type: none"> Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	NA
<ul style="list-style-type: none"> Original applicant-proposed labeling 	NA
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	NA
❖ Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> Most-recent division-proposed labels (only if generated after latest applicant submission) 	None
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	Included
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)	<input type="checkbox"/> DMETS <input type="checkbox"/> DSRCS <input checked="" type="checkbox"/> DDMAC 18Jul06 <input type="checkbox"/> SEALD <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	27Nov06-RPM Review 12May06Filing Meeting
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> • Center Director's Exception for Review memo • If AP: OC clearance for approval 	
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) • Incoming submission documenting commitment 	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Included
❖ Internal memoranda, telecons, email, etc.	Included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) • Pre-NDA/BLA meeting (<i>indicate date</i>) • EOP2 meeting (<i>indicate date</i>) • Other (e.g., EOP2a, CMC pilot programs) 	NA <input type="checkbox"/> No mtg 30Jan06 <input checked="" type="checkbox"/> No mtg None
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date of Meeting • 48-hour alert or minutes, if available 	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	None
CMC/Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	CMC Review #1-27Sep06 CMC Review #2-29Nov06 Initial Quality Assessment-5Apr06.
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> • <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) • <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) • <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	27Sep06 None None
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) 	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	Dr. Charles Resnick-8May06
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	None
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	1Dec06 -Dr. Thomas Marciniak
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	None
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	None
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
• Clinical Studies	None
• Bioequivalence Studies	28Nov06
• Clin Pharm Studies	None
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Dr. Carol Noory: 1Nov06

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) Or it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) And no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) And all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 22-026	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: None proposed Established Name: Amlodipine Besylate Orally Disintegrating Tablets Dosage Form: 2.5 mg, 5 mg, and 10 mg RPM: Denise M. Hinton		Applicant: Synthron Pharmaceuticals, Inc.
NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Division: DCRP Phone # (301) 796-1090
(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Norvasc (amlodipine besylate) Provide a brief explanation of how this product is different from the listed drug. Orally disintegrating tablet <input type="checkbox"/> If no listed drug, check here and explain: Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct. <input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date: 27Nov06
❖ User Fee Goal Date ❖ Action Goal Date (if different)		28Sep07 27Sep07
❖ Actions		
<ul style="list-style-type: none"> • Proposed action 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (specify type and date for each action taken) 		<input type="checkbox"/> None AE on 1Dec06
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics

Review priority: Standard Priority
 Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:

- Fast Track
- Rolling Review
- CMA Pilot 1
- CMA Pilot 2

Orphan drug designation

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 - Restricted distribution (21 CFR 314.520)
- Subpart I
- Approval based on animal studies

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 - Restricted distribution (21 CFR 601.42)
- Subpart H
- Approval based on animal studies

NDAs and NDA Supplements:

OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)

• Applicant is on the AIP

Yes No

• This application is on the AIP

Yes No

- Exception for review (*file Center Director's memo in Administrative Documents section*)
- OC clearance for approval (*file communication in Administrative Documents section*)

Yes No

Yes Not an AP action

❖ Public communications (approvals only)

• Office of Executive Programs (OEP) liaison has been notified of action

X Yes No

• Press Office notified of action

X Yes No

• Indicate what types (if any) of information dissemination are anticipated

- None
- FDA Press Release
- FDA Talk Paper
- CDER Q&As
- Other

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	Dr. Norman Stockbridge 29Nov06
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	NA
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	Included-30Aug07
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	Included-21Sep07
• Original applicant-proposed labeling	Included
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Included
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	None
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	Included-21Sep07
• Original applicant-proposed labeling	Included
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Included
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	NA
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	NA
• Original applicant-proposed labeling	NA
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (full color carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	None
• Most recent applicant-proposed labeling	Included
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)	<input type="checkbox"/> DMETS <input type="checkbox"/> DSRCS <input checked="" type="checkbox"/> DDMAC 18Jul06 <input type="checkbox"/> SEALD <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Documents

❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	27Nov06-RPM Review 12May06Filing Meeting
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	NA
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> -Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) Incoming submission documenting commitment 	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Included
❖ Internal memoranda, telecons, email, etc.	Included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) Pre-NDA/BLA meeting (<i>indicate date</i>) EOP2 meeting (<i>indicate date</i>) Other (e.g., EOP2a, CMC pilot programs) 	NA <input type="checkbox"/> No mtg 30Jan06 <input checked="" type="checkbox"/> No mtg None
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

CMC/Product Quality Information

❖ CMC/Product review(s) (<i>indicate date for each review</i>)	CMC Expiry 11Jul07 CMC Review #1-27Sep06 CMC Review #2-29Nov06 Initial Quality Assessment-5Apr06
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	27Sep06 None None
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>).	<input checked="" type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 29Nov06 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	Dr. Charles Resnick-8May06
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	None
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	31Aug07
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	1Dec06 -Dr. Thomas Marciniak
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	None
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	None
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summaries (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
• Clinical Studies	None
• Bioequivalence Studies	28Nov06/21May07
• Clin Pharm Studies	None
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Dr. Carol Noory: 1Nov06/25Apr07

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Denise Hinton

9/27/2007 01:58:30 PM

Hinton, Denise

From: Colangelo, Kim M
Sent: Wednesday, August 29, 2007 1:56 PM
To: Hinton, Denise
Subject: RE: NDA 22026 amlodipine besylate orally disintegrating tablets

Hi Denise,

this application is cleared for action - yippee! However, please update the filing review/Appendix B for the record, especially given the history for this application... I also note that additional revisions were listed from our last clearance round, so if those were not incorporated previously (I tried to go look in DFS myself but it is "stuck") please make those revisions as well (and if you need them I am happy to resend them!)

Kind regards,
Kim

From: Hinton, Denise
Sent: Wednesday, August 15, 2007 8:38 AM
To: Colangelo, Kim M; Weiner, Janice
Subject: RE: NDA 22026 amlodipine besylate orally disintegrating tablets

Probably on or before 7Sep07. We have to finalize the labeling and the next meeting is on 30Aug.

Thanks,

Denise

From: Colangelo, Kim M
Sent: Tuesday, August 14, 2007 4:09 PM
To: Hinton, Denise; Weiner, Janice
Subject: RE: NDA 22026 amlodipine besylate orally disintegrating tablets

Denise,

When are you planning to take an action?

From: Hinton, Denise
Sent: Tuesday, August 14, 2007 12:04 PM
To: Weiner, Janice
Cc: Colangelo, Kim M
Subject: RE: NDA 22026 amlodipine besylate orally disintegrating tablets

Thank you. We are finalizing the labeling for this application and will take an action prior to the goal date. I spoke with the PM, Margaret Simoneau, from DMEP with regard to their 505(b)2 application for _____ They had the same DSI issue re: the repeat BE study. They will be taking an action next month as well.

Thanks again.

b(4)

Denise

From: Weiner, Janice
Sent: Tuesday, July 31, 2007 12:19 PM
To: Hinton, Denise
Cc: Colangelo, Kim M
Subject: RE: NDA 22026 amlodipine besylate orally disintegrating tablets

Thanks Denise.

In follow up to my earlier correspondence, I have confirmed that the pending litigation and citizen petitions do not bear on issues related to this 505(b)(2) application. As noted below, the '303 patent (claims 1-3 of which were found to be invalid by the Court of Appeals for the Federal Circuit) does not currently appear in the Orange Book, having been delisted by FDA at Pfizer's request on or about June 22, 2007. As a result, the '303 patent and pediatric exclusivity that had attached to that patent would no longer delay approval of a 505(b)(2) application that contained a Paragraph III certification to the '303 patent.

b(4)

With reference to the sponsor's request for expeditious approval, I can comment insofar as the '303 patent and pediatric exclusivity that had attached to that patent would no longer delay approval. I am unaware of other issues that the Division may be evaluating and, of course, defer to the Division regarding the timing of an action on an application.

Should you have any questions, please do not hesitate to contact me. Thank you.

-- Janice

From: Hinton, Denise
Sent: Tuesday, July 31, 2007 10:59 AM
To: Weiner, Janice
Subject: RE: NDA 22026 amlodipine besylate orally disintegrating tablets

The goal date is September 27, 2007.

Thanks,

Denise

From: Weiner, Janice
Sent: Thursday, July 26, 2007 8:21 PM

<< File: ADP-ODT A-004 FDA Cover Ltr (3/27/07).pdf >>

<< File: PDF AE Letter.pdf >>
Thank you,

Denise

Denise Hinton
Commander, US Public Health Service
Regulatory Project Manager
Division of Cardiovascular and Renal Products
Center for Drug Evaluation and Research
Food and Drug Administration
Office (301) 796-1090
Fax (301) 796-9838

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-026

Supplement #

Efficacy Supplement Type SE-

Trade Name: None submitted at present
Established Name: amlodipine besylate orally disintegrating tablets
Strengths: 2.5 mg, 5 mg and 10 mg Tablets

Applicant: Synthron Pharmaceuticals, Inc.
Agent for Applicant: Michael H. Hinckle

Date of Original Application: January 31, 2006
Date and Receipt of Original Application: February 1, 2006
Date and Receipt of Resubmission: March 27, 2007
Date clock started after UN: NA
Date of Filing Meeting: March 21, 2006
Filing Date: March 31, 2006 as April 1, 2006 is on a Saturday
Action Goal Date (optional): December 1, 2006 User Fee Goal Date: December 1, 2006
The sponsor received an Approvable Letter on December 1, 2006. On March 27, 2007 Synthron submitted a complete response to the AE letter. The goal date for the resubmission is September 27, 2007.
Indication requested: Treatment of hypertension, chronic stable angina, and confirmed or suspected vasospastic angina

Type of Original NDA: (b)(1) (b)(2) X
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR X NDA is a (b)(2) application

Therapeutic Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: **Non-fee paying 505(b)(2)** Paid Exempt (orphan, government)

Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain: Pediatric exclusivity for Norvasc (amlodipine besylate) 2.5 and 5, and 10 mg Tablets expires on September 25, 2007.
Pfizer also has a patent for the indication "for use in patients with angiographically documented coronary artery disease that expires on September 28, 2008. This indication is not relevant for this application, as the Orally Disintegrating Tablet is not labeled for this indication.
- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO
If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).
- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format? Labeling (Carton and Container labeling, package insert) and the bioequivalence report under fasting and non-fasting conditions.
Additional comments:
- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO
- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.
Additional comments:
- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, _____ Years NO
- NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.
- NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"*
- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
- NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO
- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 72,363
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) January 30, 2006 NO
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES NO
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO
- Risk Management Plan consulted to ODS/IO? N/A YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO
A trade name has not been requested at this time. Label and labeling has been submitted to DDMAC for review
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NA
YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 21, 2006

BACKGROUND: Synthron Pharmaceuticals submitted their 505(b)(2) application, dated January 31, 2006, received February 1, 2006, in paper and Common Technical Document format for NDA 22-026/amlodipine besylate Orally Disintegrating 2.5, 5, and 10 mg Tablets.

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. Synthron is seeking approval of this new dosage form of amlodipine besylate for the same indications and strengths as Norvasc. They propose to support the approval of the 505(b)(2) with the following:

- published literature with regard to amlodipine besylate active ingredient
- FDA's previous findings of the safety and efficacy of the Norvasc drug product (NDA 19-787)
- data from comparative bioavailability (i.e. bioequivalence) studies comparing the proposed 10 mg amlodipine besylate orally disintegrating tablet with the approved Norvasc 10 mg tablet in the fasting and non-fasting conditions

ATTENDEES: Norman Stockbridge, Ph.D., Thomas Marciniak, M.D., Martin Haber Ph.D., Kasturi Srinivasachar, Ph.D., Carol Noory, B.S., Denise Hinton

ASSIGNED REVIEWERS (including those not present at filing meeting):

<u>Discipline</u>	<u>Reviewer</u>	<u>Review Date</u>
Medical:	Thomas Marciniak, MD	None
Secondary Medical:	NA	
Statistical:	NA	
Pharmacology:	NA	
Statistical Pharmacology:	NA	
Chemistry:	Martin Haber, PhD	October 1, 2006
Environmental Assessment (if needed):	NA	
Biopharmaceutical:	Carol Noory, B.S.	October 1, 2006
Microbiology, sterility:	NA	
Microbiology, clinical (for antimicrobial products only):	NA	
DSI:	Sharon Gershon, Pharm.D.	October 1, 2006
Regulatory Project Management:	Denise Hinton	
Other Consults:	DDMAC	July 1, 2006

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

• Clinical site inspection needed? YES NO

• Advisory Committee Meeting needed? YES, date if known _____ NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

Bioavailability studies are being conducted at one site.

- Biopharm. inspection needed? YES NO

PHARMACOLOGY N/A FILE REFUSE TO FILE

- GLP inspection needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74.
 - Please add USP <701> in vitro disintegration testing with acceptance criteria for disintegration time of less than 30 seconds to the drug product regulatory specification for release and stability.

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Convey document filing issues to applicant by Day 74. The letter was issued on April 13, 2006.

Denise M. Hinton
Regulatory Project Manager, HFD-110

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
NDA 19-787 Norvasc (amlodipine besylate) 2.5, 5, and 10 mg Tablets

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO X

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? Nancy Booker YES X NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss. Synthon conducted comparative bioequivalence studies to demonstrate that their amlodipine orally disintegrating tablets are bioequivalent to the approved Norvasc (amlodipine besylate) Tablets. Synthon and Pfizer have amlodipine as their active ingredient.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This application provides for a change to an orally disintegrating formulation.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s): 4,572,909, Expires January 31, 2007 and
4,879,303 Expires September 25, 2007
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?
The proposed indication is the same as Norvasc N/A X YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4): **The applicant is not requesting 3-year exclusivity.**

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a). YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval. YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# _____ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

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/s/

Denise Hinton

7/24/2007 04:30:32 PM

CSO



Memorandum

Date: July 11, 2007
From: Martin Haber, Ph.D., Review Chemist
Through: Ramesh Sood, Ph.D., Branch I Chief, DPA-1
Subject: Dissolution Testing
To: NDA 22-026 Amlodipine Orally Disintegrating Tablets

In its 12/1/06 approvable letter, the FDA requested tightening of the dissolution specification. Specifically, the acceptance limit was requested to be changed from $Q -$ in $-$ minutes to $Q -$ in 15 minutes. Available dissolution data at a 15 minute time point from current primary stability batches was also requested. b(4)

Dissolution data was submitted in Synthon Pharmaceuticals's 3/27/07 Amendment and reviewed by Dr. Carol Noory of the Office of Clinical Pharmacology and Biopharmaceutics. In her review dated 4/25/07, Dr. Noory found that the dissolution data supported a 15 minute time point and again requested that the firm tighten the dissolution specification, since Synthon was reluctant initially to make this change.

In their 6/13/07 Amendment, Synthon Pharmaceuticals, Inc. provides a commitment to perform release and stability dissolution testing as recommended by the Agency, changing the specification to provide for a 15 minute time point. The stability protocol was not changed because it references the drug product specifications which incorporate the change.

Stability data supports an expiry period of 24 months. Specifically, regarding dissolution at the 15 minute time point, most observed values are between 90 and 100%. Stability dissolution data is provided for time points of 3, 6, 10, 15, 20, 30 and 45 minutes. Occasional isolated dissolution failures at 15 minutes were observed at Stage 1 (Each unit of 6 is not less than $Q +$ $-$ in this case). All dissolution testing passed at Stage 2 (Average of 12 units is $\geq Q -$ and no unit is less than $Q -$ $-$ if the 10 and 15 minute time points are used to increase the sample size. All lots are not expected to pass Stage 1. b(4)

Based on these results, this application is recommended for "Approval" from CMC perspective with an acceptance of the proposed 24 month expiration period for the drug product.

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/s/

Martin Haber
7/11/2007 12:27:28 PM
CHEMIST

Ramesh Sood
7/11/2007 02:48:06 PM
CHEMIST

2 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Amalia Himaya
5/21/2007 11:12:18 AM
CSO

16 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Memorandum

Date: November 30, 2006
From: Martin Haber, Ph.D., Review Chemist
Through: Ramesh Sood, Ph.D., Chief, Branch I
Subject: Acceptable OC Recommendation and Stability Data
To: NDA 22-026

Regarding facilities inspections, OC made an overall Acceptable recommendation on 11/29/06.

Because OCP has recommended a shorter dissolution testing time (e.g., 15 minutes) in place of ~~30~~ minutes proposed in the NDA, the applicant will be requested in the NDA Action letter to supply available dissolution stability data at a 15 minute time point for the primary stability batches and to revise their stability protocol to collect dissolution data at 15 minutes for the current stability batches and future batches.

b(4)

R/D Init by: Dr. Ramesh Sood, Chief, DPAI, BI

Amlodipine besylate
2.5 mg, 5 mg, and 10 mg
Orally Disintegrating Tablets
Synthon Pharmaceuticals, Inc.

Method Validation

As written on page 34 of Martin Haber's review dated September 28, 2006, method validation by FDA labs is not required since only traditional methods are used.



NDA 22-026

INFORMATION REQUEST LETTER

Synthon Pharmaceuticals, Inc.
Attention: Michael H. Hinckle
VP and General Counsel
9000 Development Drive
P.O. Box 110487
Research Triangle Park, NC 27709

Dear Mr. Hinckle:

Please refer to your January 31, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amlodipine Besylate Orally Disintegrating Tablets.

We also refer to your submissions dated January 31, 2006 and June 8, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The DMF: — for "Amlodipine Besylate Monohydrate" was found inadequate.
2. Based on the batch data, tighten your proposed acceptance limits for total impurities. Provide an updated specifications table.
3. Provide updated stability data to justify the proposed 24 month expiration date.
4. In the carton labels, the proposed established name contains the salt form amlodipine besylate, which does not agree with the strength value which is based on the parent base. Please change the established name in parenthesis to amlodipine so that the established name is consistent with the labeled strength.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
9/27/2006 04:59:37 PM

MEMORANDUM

To: Denise Hinton
Division of Cardiovascular and Renal Products, HFD-110

From: Lisa Hubbard, R.Ph., Senior Regulatory Review Officer
Iris Masucci, Pharm.D., Label Reviewer
DDMAC, HFD-42

Date: July 18, 2006

Re: Comments on draft labeling:
NDA 22-026
Amlodipine besylate 2.5, 5, and 10 mg
Orally disintegrating tablets (ODT)

DDMAC has reviewed the proposed package insert for NDA 22-026 (amlodipine besylate 2.5, 5 and 10 mg orally disintegrating tablets) and offer the following comments with regard to promotional considerations:

b(4)

b(4)

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/s/

Lisa Hubbard
7/18/2006 01:59:09 PM
DDMAC REVIEWER



NDA 22-026

FILING COMMUNICATION

Synthon Pharmaceuticals, Inc.
Attention: Michael Hinckle
9000 Development Drive
P.O. Box 110487
Research Triangle Park, North Carolina 27709

Dear Mr. Hinckle:

Please refer to your January 31, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for amlodipine besylate 2.5, 5 and 10 mg Orally Disintegrating Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on April 2, 2006 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue and request that you submit the following information:

- Please add USP <701> in vitro disintegration testing with acceptance criteria for disintegration time of less than 30 seconds to the drug product regulatory specification for release and stability.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please call Ms. Denise M. Hinton, Regulatory Project Manager, at (301) 796-1090.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal
Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Denise Hinton
4/13/2006 11:05:07 AM

Norman Stockbridge
4/13/2006 01:45:18 PM



NDA 22-026

NDA ACKNOWLEDGMENT

Synthon Pharmaceuticals, Inc.
Attention: Mr. Michael H. Hinckle
9000 Development Drive
P.O. Box 110487
Research Triangle Park, North Carolina 27709

Dear Mr. Hinckle:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	Amlodipine besylate oral disintegrating 2.5, 5, and 10 mg Tablets
Review Priority Classification:	Standard (S)
Date of Application:	January 31, 2006
Date of Receipt:	February 1, 2006
Our Reference Number:	NDA 22-026

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 2, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 1, 2006.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request

for a waiver of pediatric studies for this application. We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products, Room 4156
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call:

Ms. Denise Hinton
Regulatory Health Project Manager
(301) 796-1090

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
3/2/2006 08:23:41 AM

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Synthon Pharmaceuticals, Inc.
9000 Development Drive
P. O. Box 110487
Research Triangle Park, North Carolina 27709

2. TELEPHONE NUMBER (Include Area Code)

(919) 493-6006

3. PRODUCT NAME

Amlodipine besylate Orally Disintegrating Tablets

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
 YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA)

6. USER FEE I.D. NUMBER

N/A

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Paperwork Reduction Project (HFM-99)
1 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE

Michael H. Hinckle, VP and General Counsel

DATE

1/31/2006



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 72,363

Synthon Pharmaceuticals, Inc.
Attention: Kamali Chance, MPH, PhD, RAC
9000 Development Drive
P.O. Box 110487
Research Triangle Park, North Carolina 27709

Dear Dr. Chance:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for amlodipine orally disintegrating 2.5, 5 and 10 mg Tablets.

We also refer to your amendments dated November 16, 2005 (serial # 003), December 13, 2005 (serial # 004), and January 5, 2006 (serial # 005), containing a meeting request and background documents with regard to your proposed 505(b)2 application for an orally disintegrating tablet formulation that is currently marketed by Pfizer under the trade name of Norvasc.

We note that you are seeking approval for all of the indications that are currently approved for the Norvasc drug product (hypertension, chronic stable angina, and vasospastic angina). You have committed to file appropriate patent certifications as you plan to rely upon the Agency's previous determination of the safety and effectiveness of Norvasc (amlodipine besylate) and will refrain from labeling exclusive patient populations until such exclusivity expires. We also acknowledge your proposal to conduct bioequivalence studies to show therapeutic equivalence.

We have completed the review of your submissions and are providing the answers to your questions as follows.

1. Will Synthon's bioequivalence data support NDA approval of the proposed drug product?

Your bioequivalence studies (one under fasting conditions, the other one under fed conditions) are acceptable as written.

2. Will the Division grant a "biowaiver" for the 2.5 mg and 5 mg tablet strengths based on proportional formulation, linear kinetics, and dissolution testing?

A biowaiver may be granted for the 2.5- and 5-mg tablet strengths provided the dissolution profiles are considered to be similar.

3. Does the Division agree with Synthon's conclusion that the application will be exempt from user fees because it involves a "molecular entity" that has been previously approved for the same "indications of use"?

Based on a comparative review of your proposed product labeling submitted on January 6, 2006 against Pfizer's last approved labeling for Norvasc, there are no comparative claims or new "indications for a use"; therefore, we expect your 505(b)2 application will be exempt from user fees if the same January 6, 2006, labeling is provided in your proposed NDA. When you submit your NDA, please include annotated labeling so that we can be assured that your 505(b)(2) application is still exempt from fees.

If you have further questions with regard to user fees, please contact Mr. Mike Jones, Office of Regulatory Policy at (301) 594-2041.

4. Will the Division accept the application for filing with 6 months of accelerated and real time stability data?

The Division recommends the long-term testing cover a *minimum* of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Final expiration is dependent upon the acceptability of criteria and data.

In order to comply with Q1A (R2) Stability Testing of New Drug Substances and Products and Guidance for Review Staff and Industry Good Review Management Principles and Practices for PDUFA Products, you should provide a complete application at the time of initial submission to limit the need for unsolicited or unexpected amendments during the review process. Significant omissions lead to requests for amendments or more data and could delay first cycle approval. An application is not considered complete if it meets the regulatory criteria for filing, but lacks important information needed for approval.

If you have any questions, please call:

Ms. Denise M. Hinton
Regulatory Health Project Manager
(301) 796-1090

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
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/s/

Norman Stockbridge
1/30/2006 08:56:19 AM