# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-107**

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

# 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***

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
*See OMB Statement on Page 3.*

NDA NUMBER
22-107

NAME OF APPLICANT / NDA HOLDER
Novartis Pharmaceuticals Corporation

***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)
Tekturna-HCT (proposed)

| ACTIVE INGREDIENT(S) | STRENGTH(S) |
|---|---|
| Aliskiren and Hydrochlorothiazide | 150/12.5 mg, 150/25 mg, 300/12.5 mg and 300/25 mg (Aliskiren/HCTZ respectively) |

DOSAGE FORM
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 | b. Issue Date of Patent | c. Expiration Date of Patent |
|---|---|---|
| 5,559,111 | 9/24/1996 | 4/4/2015 |

| d. Name of Patent Owner | Address *(of Patent Owner)* | |
|---|---|---|
| Novartis Corporation | 608 5th Avenue | |
| | City/State: New York, NY | |
| | ZIP Code: 10020 | FAX Number *(if available)*: 212-246-0185 |
| | Telephone Number: 212-307-1122 | 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



PSC Media Arts (301) 443-1090 EF

***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)*<br>9 | 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.)*<br>Method of treating hypertension | |

## 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 |
|---|---|
| Gregory Ferraro | 1/4/2007 |

**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<br>Gregory Ferraro | |
| Address<br>One Health Plaza | City/State<br>East Hanover, NJ |
| ZIP Code<br>07936 | Telephone Number<br>(862) 778 7831 |
| FAX Number *(if available)*<br>(973) 781-8064 | E-Mail Address *(if available)*<br>gregory.ferraro@novartis.com |

# 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.


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# EXCLUSIVITY SUMMARY

NDA # 22-107 SUPPL # HFD # 110

Trade Name Tekturna HCT Tablets

Generic Name aliskiren/hydrochlorothiazide

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known

**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)(1)

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.

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:

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# N/A

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# 21-985 Aliskiren

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:

Study 0014: Effect of the combination of Aliskiren and Hydrochlorothiazide on daytime systolic blood pressure measured by 24-Hour Ambulatory Blood Pressure Monitoring Following Once-a-Day Administration of 150mg of Aliskiren alone and in combination with 25 mg Hydrochlorothiazide in Patients with Mild to Moderate Hypertension.

Study 2204: An 8-week, double-blind, multicenter, randomized, multifactorial, placebo-controlled, parallel-group study to evaluate the efficacy and safety of aliskiren administered alone and in combination with hydrochlorothiazide in patients with essential hypertension.

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 ☒ |

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 0014: Effect of the combination of Aliskiren and Hydrochlorothiazide on daytime systolic blood pressure measured by 24-Hour Ambulatory Blood Pressure Monitoring Following Once-a-Day Administration of 150mg of Aliskiren alone and in combination with 25 mg Hydrochlorothiazide in Patients with Mild to Moderate Hypertension.

Study 2204: An 8-week, double-blind, multicenter, randomized, multifactorial, placebo-controlled, parallel-group study to evaluate the efficacy and safety of aliskiren administered alone and in combination with hydrochlorothiazide in patients with essential hypertension.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

| | | |
|---|---|---|
| Investigation #1 | | ! |
| | | ! |
| IND # 75,176 | YES ☒ | ! NO ☐ |
| | | ! Explain: |

| | | |
|---|---|---|
| Investigation #2 | | ! |
| | | ! |
| IND # | YES ☐ | ! NO ☐ |
| | | ! Explain: |

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

| | |
|---|---|
| Investigation #1 | ! |
| | ! |
| YES ☐ | ! NO ☐ |
| Explain: | ! Explain: |
| N/A | |

| | |
|---|---|
| Investigation #2 | ! |
| | ! |
| YES ☐ | ! NO ☐ |
| Explain: | ! 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: John David
Title: RPM
Date: 1/18/08

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Director, Division of Cardiovascular and Renal Products

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

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

/s/

Norman Stockbridge
1/18/2008 02:32:14 PM

# PEDIATRIC PAGE

**(Complete for all filed original applications and efficacy supplements)**

**NDA/BLA # : 22-107** **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

**Stamp Date: 3/20/07** **PDUFA Goal Date: 1/20/08**

**HFD 110** **Trade and generic names/dosage form: Tekturna HCT (aliskiren/hydrochlorothiazide) Tablets**

**Applicant: Novartis Pharmaceuticals Corp.** **Therapeutic Class: antihypertensive**

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

XX **Yes. Please proceed to the next section.**
☐ **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): 1**

**Indication #1: Treatment of hypertension with refractory to monotherapy**

**Is this an orphan indication?**

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

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

XX **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**
X **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.*

**This page was completed by: John David**

***{See appended electronic signature page}***

**Regulatory Project Manager**

**cc: NDA 22-107**
**HFD-960/ Rosemary Addy or Grace Carmouze**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**
**(revised 6-23-2005)**



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

/s/
---
John David
1/15/2008 08:37:03 AM

**NDA 22-107**

Tekturna HCT® (aliskiren-hydrochlorothiazide) Tablets

New Drug Application

## Debarment Certification

In compliance with the Generic Drug Enforcement act of 1992, Novartis Pharmaceuticals Corporation certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

Kimberly Dickerson

Kimberly Dickerson, Pharm. D
Associate Director
Drug Regulatory Affairs

01/25/2007
Date

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009.

*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).

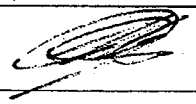
*Please mark the applicable checkbox.*

☒ (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 spreadsheet | |
| | |
| | |

☐ (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 | TITLE |
|---|---|
| Mathieu Ghadanfar, MD | Global Brand Medical Director, Tekturna |
| **FIRM / ORGANIZATION** | |
| Novartis Pharmaceuticals Corporation | |
| **SIGNATURE**  | **DATE** January 12, 2007 |

**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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

# DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009

*TO BE COMPLETED BY APPLICANT*

The following information concerning [redacted], who participated b(6)
*Name of clinical investigator*

as a clinical investigator in the submitted study SPP100A2306
*Name of clinical study*, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

*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 |
|---|---|
| Mathieu Ghadanfar, MD | Global Brand Medical Director |
| FIRM / ORGANIZATION: Novartis Pharmaceuticals Corporation | |
| SIGNATURE | DATE: January 19, 2007 |

**Paperwork Reduction Act Statement**

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

[redacted] b(6)

19 DEC 04 17:49:25 CST

To Whom It May Concern,

Pursuant to 63 FR 7271, 21 CFR Parts 541. To 54.8, and a Form 10-B ( Novartis / CERTIFICATION/DISCLOSURE FOR 1 / Financial Disclosure by Clinical Investigators," attached) completed this day by the undersigned, it is my duty to report that, since February 2, 1999, I have received "significant payments of other sorts" exceeding $25,000 from Novartis Pharmaceuticals Corporation. These payments were honoraria and travel expenses for lectures and other educational activities, funded either indirectly (e.g., through hospitals, medical societies or other third-party vendors) or directly from Novartis Pharmaceuticals Corporation, its assigns, subsidiaries, and/or independent contractors.

In addition, it is likely (if not absolutely certain) that during the upcoming year, the Department of Preventive Medicine at RUSH University Medical Center (or under its former legal name, RUSH-Presbyterian-St. Luke's Medical Center), as well as its other Departments within the institution of which I have no direct knowledge, will accrue grants and/or other payments for clinical studies supported by Novartis Pharmaceuticals Corporation (including the recently reported VALUE and others) that exceeded or will exceed $25,000 during the next calendar year.

We trust this information is helpful to you.

Sincerely yours,

[redacted] b(6)

**Novartis**

**CERTIFICATION/DISCLOSURE FORM**

**Financial Disclosure by Clinical Investigators**

1. Study Name: A 26 week, double-blind, randomized multicenter, parallel group, active-controlled study comparing aliskiren to ramipril with optional addition of hydochlorothiazide, followed by a 4 week double-blind, randomized, placebo-controlled withdrawal in patients with essential hypertension

2. Protocol number: CSPP100A2306

3. Investigator Subinvestigator ☒

4. Investigator/subinvestigator Name: [redacted] b(6)

5. Address: [redacted]

6. Telephone: [redacted] 7. Fax: [redacted]

8. Indicate by marking Yes or No if any of the financial interests or arrangements with Novartis of concern to FDA (and describe below) apply to you, your spouse, or dependent children:

| | | |
|---|---|---|
| Yes ☐ | No ☒ | Financial Arrangements whereby the value of the compensation could be influenced by the outcome of the study. This could include, for example, compensation that is explicitly greater for a favorable outcome, or compensation to the investigator in the form of an equity interest in the sponsor or in the form of compensation tied to sales of the product such as a royalty interest.<br>If yes, please describe: |
| Yes ☒ | No ☐ | Significant payments of other sorts, excluding the costs of conducting the study or other clinical studies. This could include, for example, payments received by the investigator to support activities that have a monetary value greater than $25,000 (i.e. a grant to the investigator or the institution to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria).<br>If yes, please describe: Please see attached letter dated 19 dec 04 17:48 CST. |
| Yes ☐ | No ☒ | A proprietary or financial interest in the test product such as a patent, trademark, copyright, or licensing agreements.<br>If yes, please describe: |
| Yes ☐ | No ☒ | A significant equity interest in the sponsor of the study. This would include, for example, any ownership interest stock options, or other financial interest whose value cannot be easily determined through reference to public prices, or any equity interest in a publicly traded company exceeding $50,000.<br>If yes, please describe: |

or

☐ I hereby certify that none of the financial interest or arrangements listed above exist for myself, my spouse, or my dependent children.

In accordance with 21 CFR Parts 54.1 to 54.8, I declare that the information provided on this form is, to the best of my knowledge and belief, true, correct, and complete. Furthermore, if my financial interests and arrangements, or those of my spouse and dependent children, change from the information provided above during the course of the study or within one year after the last patient has completed the study as specified in the protocol, I will notify(company name) promptly.

9. Name: (please print) [redacted] b(6)

Signature [redacted]

10. Date 19 DEC 04 17:56 CST

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-107

**NDA ACKNOWLEDGMENT**

Novartis Pharmaceuticals Corporation
Attention: Kimberly D. Dickerson, Pharm.D.
Associate Director
Drug Regulatory Affairs
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Dr. Dickerson:

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: Tekturna HCT® (aliskiren-hydrochlorothiazide) 150/12.5mg, 150/25mg, 300/12.5mg and 300/25mg Tablets

Review Priority Classification: Standard (S)

Date of Application: March 19, 2007

Date of Receipt: March 20, 2007

Our Reference Number: NDA 22-107

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 May 19, 2007, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 20, 2008.

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.

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
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact:

Quynh M Nguyen, Pharm.D.
Regulatory Project Manager
(301) 796 - 0510.

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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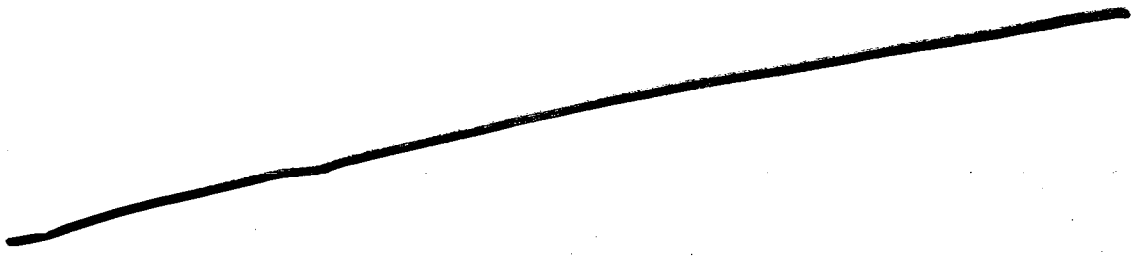
/s/

Edward Fromm
4/5/2007 08:35:27 AM

**RHPM Overview of NDA 22-107**
**Tekturna HCT (aliskiren/hydrochlorothiazide) 150/12.5 mg, 150/25 mg, 300/12.5 mg, and 300/25 mg tablets**
**January 22, 2008**

| | |
|---|---|
| Sponsor: | Novartis Pharmaceuticals Corporation |
| Type: | 4S |
| Receipt Date: | March 20, 2007 |
| User Fee Goal Date: | January 20, 2008 |
| AP Letter Issued: | January 18, 2008 |
| Final Draft Labeling: | January 18, 2008 (Enclosed in the AP letter) |

**Background**
Novartis Pharmaceuticals Corporation submitted this NDA for Tekturna HCT (aliskiren/hydrochlorothiazide) Tablets for the treatment of hypertension. NDA 21-985 for Tekturna (aliskiren) Tablets was approved on March 5, 2007. The development of Tekturna HCT Tablets was conducted under IND 62,976 (aliskiren monotherapy) and IND 75,176 (aliskiren/hydrochlorothiazide fixed dose combination). In support of approval, the sponsor has submitted results from their preclinical, clinical, clinical pharmacology, and CMC development program. The pivotal trial for this NDA submission is a multifactorial study (CSPP100A2204). The proposed doses for marketing are 150/12.5 mg, 150/25 mg, 300/12.5 mg, and 300/25 mg.



b(4)

**Office Director's Memorandum**
N/A

**Division Director's Memorandum**
Dr. Stockbridge noted in his Division Director's Memo dated January 20, 2008 support for the approval of Tekturna HCT (aliskiren/hydrochlorothiazide) Tablets for the treatment of hypertension.

**Medical Review**
In his review dated December 7, 2007, Dr. Xiao states that he recommends that Tekturna HCT, the combination of aliskiren and Hydrochlorothiazide (HCTZ), be approved for the treatment of hypertension. This combination product demonstrated clinically and statistically significant reductions in both diastolic and systolic blood pressure compared to placebo and each respective monotherapy in one randomized, double-blind, placebo-controlled trial and several other active-controlled trials. The maximum antihypertensive effect was generally attained after 4 weeks of therapy.

He noted that the adverse event profile of the combination is similar to each component monotherapy. The incidence of significant AEs identified during aliskiren monotherapy clinical development program including angioedema, and GI events are also similar in the aliskiren/HCTZ combination therapy. Regarding laboratory parameters, both aliskiren and HCTZ monotherapies increased the serum level of uric acids; the combination of aliskiren/HCTZ increased serum level of uric acid even further. There was no difference of incidence rates of gout and kidney stones in short-term studies. In the long-term open label study, however, the incidence rate of gout was 0.5% (4 cases) in the combination therapy and 0.1%

(1 case) in the aliskiren monotherapy. Difference for the incidence of kidney stones was not observed in this long-term open label study although the higher serum level of uric acid was observed in the combination therapy. Overall, AE profile is considered to be acceptable for antihypertensive therapy.

Labeling recommendations were provided during labeling meetings.

There are no mandatory phase 4 studies for this NDA.

Refer to the financial disclosure is as noted on page 24 of the medical review dated December 7, 2007.

**Pharmacology Review**
In his review dated August 31, 2007, Dr. Jagadeesh states that this NDA is approvable from the pharmacology/toxicology perspective.

He noted that although the combined administration of aliskiren hemifumarate and HCTZ did not augment any existing toxicities of the individual agents in the 13 week toxicology study, and although no new toxicities were identified, we note that the highest dose used in the toxicology study, 150:12 mg (aliskiren:HCTZ)/kg/day, was not high enough to demonstrate toxic effects that had been seen in other studies with aliskiren hemifumarate alone. In rats, this drug increased the incidence of mucosal epithelial hyperplasia in the small and large intestine at 250 or more mg aliskiren/kg/day and cecal erosion and ulceration at 750 or more mg aliskiren/kg/day. One colonic adenoma and one cecal adenocarcinoma (rare tumors in the rat strain studied) were observed in males receiving 1500 mg/kg/day for 24 months (see NDA 21,985 review). In addition, systemic exposure for aliskiren at the highest dose in the combination toxicology study was lower than the anticipated clinical exposure. This may not be a concern for humans, based on the apparent tolerance when the combination was administered in clinical trials.

**Chemistry Review**
In his review dated January 7, 2008, Dr. Ysern states that from a CMC point of view this application can be approved. He noted that all CMC pending issues have been addressed satisfactorily by the applicant (Amendments 28-Nov-2007 and 12-Dec-2007).

There are no Phase IV Commitments.

He noted that the Environmental Assessment is acceptable.

**Statistical Review**
Refer to Dr. Bai's statistical review dated October 4, 2007 in which he noted that based on Study SPP100A-2204, the one-daily oral treatment with Aliskiren in dose of 300 mg lowers blood pressure more effectively than placebo in patients with essential hypertension over 8-week treatment period. In addition, the combinations of Aliskiren and HCTZ in 150/25 mg, 300/12.5 mg and 300/25 mg doses were also found to be significantly superior to the component monotherapies in reducing msDBP. This reviewer concurred with the sponsor's findings which are: a) at least one Aliskiren monotherapy dose was superior to placebo in reducing msDBP and b) at least one combination was significantly superior overall to both component monotherapies in reducing msDBP.

**Biopharmaceutical Review**
Refer to Dr. Velazquez of the Office of Clinical Pharmacology and Biopharmaceutics review dated December 13, 2007.

There are no Phase IV Commitments.

Labeling recommendations are noted in the biopharmaceutical review.

**DSI**
No Division of Scientific Investigation was recommended for this application.

**Pediatric Rule**
The Division agreed that a waiver would be acceptable on the basis that pediatric data will not be available for each of the components at the projected time of submission (see 9/8/06 Pre-NDA Meeting Preliminary Responses).

All pediatric age group(s) are waived because studies are impossible or highly impractical.

**Labeling**
The sponsor submitted the most recent draft PI/PPI labeling on January 16, 2008 as email attachments and revised carton and container labels on December 11, 2007.

This NDA will be approved on draft labeling.

**Advisory Committee Meeting**
This application did not go before the Advisory Committee.

**Project Manager's Summary**
To my knowledge, there are no issues that might prevent taking regulatory action on this NDA.

John David, BSN, MS in HRM
Regulatory Health Project Manager

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/s/
---
John David
1/22/2008 09:25:58 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-107

**INFORMATION REQUEST LETTER**

Novartis Pharmaceuticals Corporation
Attention: Kimberly D. Dickerson, Pharm.D.
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Dickerson:

Please refer to your March 19, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tekturna HCT (aliskiren/hydrochlorothiazide) 150/12.5 mg, 150/25 mg, 300/12.5 mg, and 300/25 mg Tablets.

We also refer to your submissions dated May 11 and October 2, 2007.

We are reviewing the clinical pharmacology and labeling sections 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.

CLINICAL PHARMACOLOGY

There appears to be a higher intersubject variability in aliskiren than in most antihypertensives. (The intersubject variability can be as high as 75% and as low as 36% for Cmax, 50 to 31% for AUC). One might conclude that patients at the low end of the distribution for AUC or Cmax would be unlikely to benefit from aliskiren. While this is not a major issue with monotherapy (they will go elsewhere), they would likely continue taking an ineffective drug as part of the combination product. [redacted] b(4)

LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

A.

[redacted] b(4)

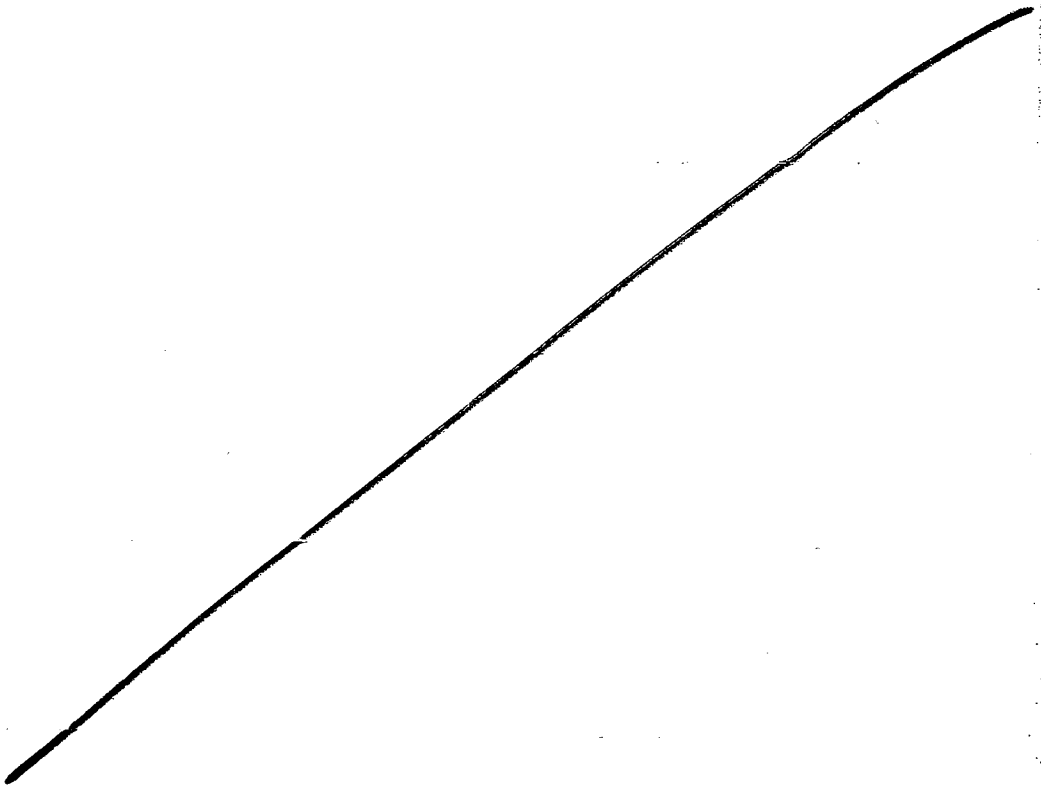
B.

C. b(4)

D. b(4)

E. b(4)

F. b(4)



If you have any questions, please contact:

Mr. John David
Regulatory Project Manager
(301) 796-1059

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/

Norman Stockbridge
11/29/2007 05:02:19 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-107

**DISCIPLINE REVIEW LETTER**

Novartis Pharmaceuticals Corporation
Attention: Kimberly D. Dickerson, Pharm.D.
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Dickerson:

Please refer to your March 19, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tekturna HCT (aliskiren/hydrochlorothiazide) 150/12.5 mg, 150/25 mg, 300/12.5 mg, and 300/25 mg Tablets.

We also refer to your submissions dated March 27, April 27, May 30 and September 17, 2007.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. The proposed dissolution acceptance criteria, Q = [redacted]% in 60 minutes for HCTZ and Q = [redacted]% in 45 minutes for SPP100, is not supported by development or stability data. Developmental batch release data indicate that full dissolution is reached at about 30 minutes or earlier (dissolution profile data) in both cases. Stability data (25 °C/60 % RH and 30 °C/65 % RH) indicate that HCTZ is fully dissolved in 60 minutes (one-point testing time). In the case of SPP100, complete dissolution is observed at 45 minutes (one-point test time for SPP100). Based on the submitted data, we recommend Q = [redacted]% in 30 minutes (0.1 M HCl, 100 rpm, 900 mL, USP apparatus 1 (basket), 37 °C) as the dissolution acceptance criteria for both active components, SPP100 and HCTZ. b(4)

   If the available dissolution profile data on stability samples do not support the recommended acceptance criterion, propose revised acceptance criterion based on the available dissolution profile data collected on stability samples for both SPP100 and HCTZ.

2. Revise the proposed acceptance criterion for the "Total Degradation Product" based on the available data collected on stability samples.

3. [redacted] b(4)

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be

provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please contact:

Mr. John David
Regulatory Project Manager
(301) 796-1059

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/

Norman Stockbridge
11/21/2007 10:25:28 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-107

Novartis Pharmaceuticals Corporation
Attention: Kimberly Dickerson, Pharm.D.
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Dr. Dickerson:

Please refer to your March 19, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tekturna HCT (aliskiren/hydrochlorothiazide) 150/12.5 mg, 150/25 mg, 300/12.5 mg, and 300/25 mg Tablets.

We also refer to your submissions dated March 27, April 16 and 27, and May 2, 4, and 11, 2007.

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 May 19, 2007 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing 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.

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 requirement. We are waiving the requirement for pediatric studies for this application.

If you have any questions, please contact:

Mr. John David
Regulatory Project Manager
(301) 796-1059

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/
---
Norman Stockbridge
5/24/2007 01:46:06 PM

# NDA REGULATORY FILING REVIEW
**(Including Memo of Filing Meeting)**

NDA # 22-107 Supplement # Efficacy Supplement Type SE-

Proprietary Name: aliskiren/hydrochlorothiazide
Established Name: Tekturna HCT Tablets
Strengths: 150/12.5 mg, 150/25 mg, 300/12.5 mg, and 300/25 mg

Applicant: Novartis Pharmaceuticals Corporation
Agent for Applicant (if applicable):

Date of Application: 3/19/07
Date of Receipt: 3/20/07
Date clock started after UN: N/A
Date of Filing Meeting: 5/8/07
Filing Date: 5/19/07
Action Goal Date (optional): User Fee Goal Date: 1/20/08

Indication(s) requested: Treatment of hypertension.

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
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 or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 4
Other (orphan, OTC, etc.)

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

User Fee Status: Paid ☒ # PD3007115 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 by contacting the User Fee staff in the Office of Regulatory Policy. 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 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 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 any approved (b)(1) or (b)(2) application? YES ☒ NO ☐
  If yes, explain: NDA 21-985 for Tekturna (aliskiren) Tablets was approved 3/5/07 and granted 5-year exclusivity for a NME.

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- 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 ☐
  If no, explain:

- 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:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as a partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☒
   This application is: All electronic ☐ Combined paper + eNDA ☒
   This application is in: NDA format ☒ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

   **If an eNDA, all forms and certifications must be in paper and require a signature.**

   If combined paper + eNDA, which parts of the application were submitted in electronic format?
   1) Table of Contents
      Cover Letter – paper copy also with original signature
      Form FDA 356h – paper copy also with original signature
   2) Labeling
   3) Summary
   4) CMC
   5) Nonclinical Pharmacology and Toxicology
   6) Human Pharmacology and Bioavailability/Bioequivalence

8) Clinical
10) Statistical
11) Case Report Tabulations (CRTs)
12) Case Report Forms (CRFs)
13) Patent Information – paper copy also with original signature
14) Patent Certification – paper copy also with original signature
16) Debarment Certification – paper copy also with original signature
17) Field copy Certification – paper copy also with original signature
18) User Fee Cover Sheet – paper copy also with original signature
19) Financial Disclosure – paper copy also with original signature
20) Other

**Additional comments:** None.

3. This application is an eCTD NDA. YES ☐ NO ☒
**If an eCTD NDA, 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 . . . ."*
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES ☐ NO ☒
**Additional comments:** Division granted waiver of pediatric studies (see 9/8/06 Pre-NDA Meeting Preliminary Responses).
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO ☐
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
**(Forms 3454 and/or 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) YES ☒ NO ☐

- PDUFA and Action Goal dates correct in tracking system? 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. YES ☒ NO ☐

- List referenced IND numbers: 62,976 and 75,176

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) 2/11/04 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) See 9/8/06 Pre-NDA Mtg Preliminary Responses and 1/16/07Advice Letter NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) 6/3/04 (see also 7/12/04 Tcon Minutes) NO ☐
  If yes, distribute letter and/or relevant minutes before filing meeting.

## Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  **If no, explain:**

  Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request: ***N/A***

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  PPI submitted N/A ☐ YES ☒ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES ☒ NO ☐
  Note: During the 5/8/07 Filing Meeting, it was determined that an RMP was not needed (see attached minutes of filing meeting).

- 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 or OTC application:** *N/A*

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A ☒ 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 EA officer, OPS? YES ☒ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒
- If a parenteral product, consulted to Microbiology Team? N/A ☒

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 5/8/07

**NDA #:** 22-107

**DRUG NAMES:** Tekturna HCT (aliskiren/hydrochlorothiazide) Tablets

**APPLICANT:** Novartis Pharmaceuticals Corporation

**BACKGROUND:** This NDA provides for Tekturna HCT (aliskiren/hydrochlorothiazide) Tablets for the treatment of hypertension. NDA 21-985 for Tekturna (aliskiren) Tablets was approved on March 5, 2007. The development of Tekturna HCT Tablets was conducted under IND 62,976 (aliskiren monotherapy) and IND 75,176 (aliskiren/hydrochlorothiazide fixed dose combination).

In support of approval, the sponsor has submitted results from their preclinical, clinical, clinical pharmacology, and CMC development program. The pivotal trial for this NDA submission is a multifactorial study (CSPP100A2204). The proposed doses for marketing are 150/12.5 mg, 150/25 mg, 300/12.5 mg, and 300/25 mg.

An Environment Assessment (EA) was submitted pursuant to 21 CFR Part 25.

PLR and SPL labeling were submitted. SEALD is aware of the NDA submission. Consult requests were sent to DDMAC for review of the proposed labeling (carton, container, PI, and PPI) and OSE for review of the tradename, proposed labeling (carton, container, PI, PPI), and RMP on 5-7-07. During the meeting, Mary Dempsey of OSE stated that the RMP consists of labeling and routine pharmacovigilance and Dr. Stockbridge agreed that an RMP was not needed and therefore, an OSE review of the RMP was not needed. OSE will place a Memo to the File into DFS stating this.

**ATTENDEES:** Norman Stockbridge, Thomas Marciniak, Shen Xiao, Charles Resnick, Gowra Jagadeesh, Lydia Velazquez, Mary Dempsey, Edward Fromm, John David, Quynh Nguyen

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

| Discipline/Organization | Reviewer | Expected Completion Date |
|---|---|---|
| Medical: | Shen Xiao | 10/31/07 |
| Secondary Medical: | N/A | |
| Statistical: | Steven Bai | 10/31/07 |
| Pharmacology: | Gowra Jagadeesh | 10/31/07 |
| Statistical Pharmacology: | N/A | |
| Chemistry: | Xavier Ysern | 10/31/07 |
| Environmental Assessment (if needed): | | |
| Biopharmaceutical: | Lydia Velazquez | 11/20/07 |
| Microbiology, sterility: | N/A | |
| Microbiology, clinical (for antimicrobial products only): | N/A | |
| DSI: | N/A | |
| OPS: | | |
| Regulatory Project Management: | John David | |
| Other Consults: | OSE, DDMAC, SEALD | |

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

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☐ NO ☒
  If no, explain: Per the Division Director, a DSI inspection is not needed.
- 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 N/A ☐ FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☐ NO ☒

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? N/A ☐ YES ☒ NO ☐
- Sterile product? YES ☐ NO ☒
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments: The NDA is located in the EDR at: **\\CDSESUB1\NONECTD\N22107\N_000\2007-03-19**

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. List (optional):

**ACTION ITEMS:**

1. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. ☐ 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.
4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Quynh Nguyen
Regulatory Project Manager

## Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
(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.)

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) 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, and.

(3) 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) 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, or

(3) 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.



Appears This Way
On Original

**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):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☐

*If "Yes," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO ☐

*If "Yes "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval 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 ☐

(***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," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (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," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

*(b)* Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "Yes," to (c), proceed to question 7.*

***NOTE:*** *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☐

*If "No," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. 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").

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

10. Is the application for a duplicate of a listed drug whose only difference is that 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 may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made YES ☐ NO ☐

available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. 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.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 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)

☐ 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)]. OND will contact you to verify that this documentation was received.*

☐ 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):

☐ 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):

14. Did the applicant: