

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-689

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



PATENT CERTIFICATION

Not applicable

This application is not a 505(b)(2) application; therefore, the Patent Certification as described under 21 U.S.C. 355(b)(2) or (j)(2)(A) and 21 CFR 314.50(i) is not required.

**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

21-689

NAME OF APPLICANT / NDA HOLDER

AstraZeneca LP

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)

NEXIUM® I.V. (esomeprazole sodium) for Injection

ACTIVE INGREDIENT(S)

Esomeprazole sodium

STRENGTH(S)

20 mg and 40 mg Esomeprazole (21.3 mg and 42.5 mg
Esomeprazole sodium)

DOSAGE FORM

Injection

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

5,589,491

b. Issue Date of Patent

December 31, 1996

c. Expiration Date of Patent

December 31, 2013

d. Name of Patent Owner

Astra Aktiebolag (now named AstraZeneca AB)

Address (of Patent Owner)

SE-151 85 Södertälje, Sweden

City/State

Södertälje, Sweden

ZIP Code

SE-151 85

FAX Number (if available)

Telephone Number

01146855326000

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.)

1800 Concord Pike

City/State

Wilmington, DE

ZIP Code

19850-5437

FAX Number (if available)

Telephone Number

(800) 456-3669

E-Mail Address (if available)

Glenn M. Engelmann, General Counsel

AstraZeneca Pharmaceuticals LP

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

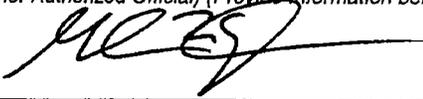
6. Declaration Certification

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



9/3/04

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

Glenn M. Engelmann, General Counsel

Address

1800 Concord Pike

City/State

Wilmington, DE

ZIP Code

19850-5437

Telephone Number

(302) 886-3244

FAX Number (if available)

(302) 886-1578

E-Mail Address (if available)

glenn.engelmann@astrazeneca.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

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1. GENERAL

a. United States Patent Number 6,143,771	b. Issue Date of Patent November 7, 2000	c. Expiration Date of Patent May 27, 2014
d. Name of Patent Owner AstraZeneca AB	Address (of Patent Owner) SE-151 85 Södertälje, Sweden	
	City/State Sodertalje, Sweden	
	ZIP Code SE-151 85	FAX Number (if available)
	Telephone Number 01146855326000	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) ☞ Glenn M. Engelmann, General Counsel ☞ AstraZeneca Pharmaceuticals LP	Address (of agent or representative named in 1.e.) 1800 Concord Pike	
	City/State Wilmington, DE	
	ZIP Code 19850-5437	FAX Number (if available)
	Telephone Number (800) 456-3669	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? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		

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STRENGTH(S)

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1. GENERAL

a. United States Patent Number

4,738,974

b. Issue Date of Patent

April 19, 1988

c. Expiration Date of Patent

April 19, 2005

d. Name of Patent Owner

Aktiebolaget Hassle

Address (of Patent Owner)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

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)

Glenn M. Engelmann, General Counsel

AstraZeneca Pharmaceuticals LP

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

1800 Concord Pike

City/State

Wilmington, DE

ZIP Code

19850-5437

FAX Number (if available)

Telephone Number

(800) 456-3669

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.

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

1. 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) 6, 7, 8, 9, 10, 11 and 12 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.)
 The short-term treatment (up to 10 days) _____ GERD) as an alternative to oral therapy in patients when therapy with NEXIUM Delayed Release Capsules is not possible or appropriate. The recommended adult dose _____ 20 mg or 40 mg esomeprazole given once daily by injection (no less than 3 minutes) or infusion (10 to 30 minutes). _____

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

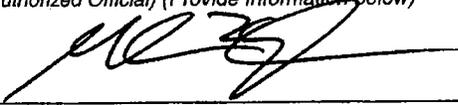
6. Declaration Certification

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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



9/3/03

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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

Glenn Engelmann, General Counsel

Address

1800 Concord Pike

City/State

Wilmington, DE

ZIP Code

19850-5437

Telephone Number

(302) 886-3244

FAX Number (if available)

(302) 886-1578

E-Mail Address (if available)

Glenn.engelmann@astrazeneca.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

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2. Drug Substance (Active Ingredient)

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- 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
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- 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
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4. Method of Use

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- 4.2 Patent Claim Number (as listed in the patent) 9, 10, 11, 13, 14 and 15 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.)
 The short-term treatment (up to 10 days) _____ (GERD) as an alternative to oral therapy in patients when therapy with NEXIUM Delayed Release Capsules is not possible or appropriate. The recommended adult dose _____ 20 mg or 40 mg esomeprazole given once daily by injection (no less than 3 minutes) or infusion (10 to 30 minutes). _____

5. No Relevant Patents

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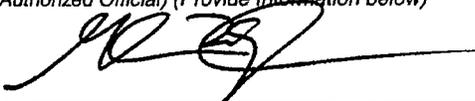
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NDA Applicant/Holder

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

Patent Owner

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EXCLUSIVITY SUMMARY for NDA # NDA 21-689 SUPPL # -----

Trade Name Nexium IV (esomeprazole) for Injection

Generic Name (esomeprazole)

Applicant Name Astra-Zeneca
HFD- 180

Approval Date 03/31/05

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES / x / NO / /
b) Is it an effectiveness supplement? YES / / NO / x /

If yes, what type (SE1, SE2, etc.)? -----

- 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 / x / 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 /x/ NO /___/

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

3 years

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

YES /___/ NO /x/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /x/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /x/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 # 21-153 Nexium (esomeprazole)Delayed-Release Capsules

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 #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S 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 /_x_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 /_x_/ 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 9:**

- (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 /_x_/

- (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 /_x_/

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:

Investigation #1, Study # D9615C00014

Investigation #2, Study #

Investigation #3, Study #

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 /_x_/

Investigation #2 YES /___/ NO /___/

Investigation #3 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:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (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 /_x_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (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"):

Investigation #__, Study # D9615C00014

Investigation #__, Study #

Investigation #__, Study #

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 # 64,865 YES /x/ 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 /___/ 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 /_x_/

If yes, explain: _____

 Melissa Furness
Signature of Preparer

 05/04/05
Date

Title: Regulatory Health Project Manager

 Dr. Joyce Korvick
Acting Division Director

 05/06/05
Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Joyce Korvick
5/5/05 01:45:04 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: NDA 21-689 Supplement Type (e.g. SE5): ----- Supplement Number: -----

Stamp Date: 09/30/04 (2nd cycle) Action Date: 03/31/05

HFD-180 Trade and generic names/dosage form: Nexium IV (esomeprazole) for Injection

Applicant: Astra Zeneca Therapeutic Class: PPI

Indication(s) previously approved: -----

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: short-term treatment (up to 10 days) of GERD patients with a history of erosive esophagitis as an alternative to oral therapy in patients when therapy with NEXIUM Delayed-Release Capsules is not possible or appropriate

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

- Yes: Please proceed to Section A.
 - No: Please check all that apply: Partial Waiver x 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: Please note that a waiver was not granted prior to the Pediatric Rule being challenged in court.

- 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:

Min <u> </u>	kg <u> </u>	mo. <u> </u>	yr. <u> </u>	Tanner Stage <u> </u>
Max <u> </u>	kg <u> </u>	mo. <u> </u>	yr. <u> </u>	Tanner Stage <u> </u>

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:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 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:

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:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337**

Attachment A

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

Indication #2: _____

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:

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:

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:

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

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337**

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

/s/

Melissa Furness
5/5/05 03:57:15 PM

ITEM 16 DEBARMENT CERTIFICATION

Re: NDA #21-689

NEXIUM[®] (esomeprazole sodium) for Injection

Debarment Certification Statement

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of AstraZeneca Pharmaceuticals LP, that we did not use and will not use in connection with this application, the services of any person in any capacity debarred under section 306 (a) or (b)

Sincerely,


VPRA

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 21-689	Efficacy Supplement Type	Supplement Number
Drug: Nexium (esomeprazole) IV for Injection		Applicant: Astra Zeneca LP
RPM: Melissa Furness		HFD-180 Phone # 301-827-7450
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): (NDA 21-153, Nexium (esomeprazole) Delayed-Release Capsules);
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		07/10/04; 03/31/05
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified <input type="checkbox"/> N/A
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified <input checked="" type="checkbox"/> N/A
❖ Exclusivity Summary (approvals only)		X

Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	12/2003
General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(x) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (x) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(x) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X
• Applicant proposed	X
• Reviews	X
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	X
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
✓ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	03/23/05; 07/29/04
❖ Clinical review(s) (indicate date for each review)	06/16/04
❖ Microbiology (efficacy) review(s) (indicate date for each review)	06/29/04
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	X
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) (indicate date for each review)	06/23/04
❖ Biopharmaceutical review(s) (indicate date for each review)	06/18/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	02/18/05; 06/25/04; 06/10/04
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	See CMC Review
• Review & FONSI (indicate date of review)	See CMC Review
• Review & Environmental Impact Statement (indicate date of each review)	See CMC Review
Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed (X) Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	06/24/04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

18 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 4

36 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 3

Furness, Melissa

From: Kummeth, George [George.Kummeth@astrazeneca.com]
Sent: Friday, March 25, 2005 9:40 AM
To: 'Furness, Melissa'
Subject: NDA 21-689 NEXIUM I.V.



ATT587345.rtf (1 KB)



proposednonannotated.doc (140 KB)



proposedannotated.doc (141 KB)



container40mg.pdf (412 KB)



container20mg.pdf (412 KB)



carton40mg.pdf (442 KB)



carton20mg.pdf (443 KB)



mmsinfo.txt (418 B)

Good Morning Melissa,

Thank you again for the productive teleconference yesterday afternoon regarding NEXIUM I.V.

I am providing to you the following attachments:

- Annotated package insert, word format. Please note the following with respect to this version of the package insert:

- We have agreed to remove all reference to the safety study in the Clinical Studies section.

- As requested in the ADVERSE REACTIONS section, we have described the skin reactions that occurred in more detail. The text now reads "Application site disorders: application site reaction (1.7%) (including mild focal erythema and pruritus at IV insertion site)."

- In the annotated version we have removed all deleted text and only included FDA's and AZ's additional text. All additions are indicated by double underlined text.

- Clean package insert, word format.

- Carton and vial labeling, pdf format. All FDA comments have been incorporated except for the _____ as space does not permit this additional text.

We are also submitting these documents to you today in an official submission on CDROM and hard copy via courier.

Best Regards,

George

George Kummeth
AstraZeneca LP
Director, Regulatory Affairs - NEXIUM
302-885-8415

4 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 1



September 10, 2003

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

Re: NDA 21-689
NEXIUM[®] I.V. (esomeprazole sodium) for Injection
Original New Drug Application

Dear Sir/Madam:

Pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act and Section 314 of Title 21 of the Code of Federal Regulations, AstraZeneca LP (AstraZeneca) is submitting an Original New Drug Application (NDA 21-689 and User Fee ID No. 4598) for NEXIUM I.V. (esomeprazole sodium) for Injection for the short-term treatment (up to 10 days) of ~~GERD~~ (GERD) as an alternative to oral therapy in patients when therapy with NEXIUM Delayed-Release Capsules is not possible or appropriate.

This NDA consists of data from a global development program, conducted in part under IND 64,865, that supports the safety and efficacy of Nexium I.V. and includes a total of 14 completed clinical studies (9 Phase I studies and 5 Phase III studies). The Phase I clinical pharmacology studies evaluated the pharmacokinetics and pharmacodynamics of intravenous esomeprazole (at various administration rates) and oral esomeprazole, as well as safety and tolerability. In 4 Phase III pharmacology studies the intravenous and oral formulations were compared with respect to pentagastrin-stimulated and basal gastric acid output in symptomatic GERD patients with or without erosive esophagitis (EE). In one Phase III study in patients with EE, the safety and EE healing rates of intravenous and oral esomeprazole 40 mg were studied.

A Type B meeting was held between AstraZeneca and FDA on December 6, 2001 to discuss the NDA submission of NEXIUM I.V. The purpose of this meeting was to discuss and reach agreement on the adequacy of the proposed clinical program and nonclinical bridging program to support an alternative dosage form for NEXIUM. The advice and recommendations provided by the Agency during this meeting were incorporated into the NEXIUM I.V. clinical and nonclinical program, including the conduct of acid-output studies and a 1-month intravenous toxicity study in dogs using continuous infusion of esomeprazole sodium. The official minutes of this meeting were issued by FDA on April 11, 2002 and are incorporated herein under Regulatory History and Organization.

An additional meeting (teleconference) was held on September 12, 2002 to discuss various CMC issues related to the NDA submission. The advice and recommendations obtained during this teleconference were incorporated into the NDA CMC documentation. AstraZeneca submitted minutes of this meeting to IND 64,865 on October 1, 2002 (Serial No. 011). As recommended by FDA during this meeting, a CMC Information Amendment was submitted to IND 64,865 on April 15, 2003 (Serial No. 015) providing various data and information to facilitate early review of the NEXIUM I.V. CMC information.

A pre-NDA background package was submitted to IND 64,865 on February 10, 2003 (Serial No. 013) that provided information pertaining to the content and format of the NEXIUM I.V. NDA. The following are major highlights from the background package regarding the content of the enclosed NDA:

- Summaries of Clinical Efficacy and Safety will be adequate and a separate ISS and ISE will not be provided.
- SAS "raw" and "analysis" datasets will only be provided for Phase III studies in this application.
- Only domain listings will be provided for review.

Research centers within the US conducted investigations under the IND regulations and followed Good Clinical Practices (GCPs) in compliance with the Institutional Review Board requirements in 21 CFR 56, and informed consent requirements in 21 CFR 50. All foreign clinical trials were conducted in accordance with GCPs, the ethical principles stated in the Declaration of Helsinki, and the laws and regulations of the country in which the study was conducted.

In accordance with Prescription Drug User Fee Act of 1992, as amended by the Food and Drug Administration Modernization Act of 1997, a check (No. 42458314) in the amount of \$533,400.00 was sent to FDA, care of Mellon Bank, Pittsburgh, PA on August 26, 2003.

The format of this NDA is consistent with 21 CFR 314.50 and with FDA guidelines for the preparation and submission of NDAs as described in the January 1999 Guidance for Industry "Providing Regulatory Submission in Electronic Format - General Considerations". Moreover, this NDA is being filed as a Common Technical Document (CTD), and follows the Guidances M4: Organization, M4Q: Quality, M4S: Safety and M4E: Efficacy of the CTD.

The first binder with electronic media contains a paper copy of the cover letter, Form FDA 356h, and a CD-ROM.

The information for this NDA is provided on a CD-ROM and the total file size is approximately 382mb. The media has been scanned using Norton Antivirus Version 8.00.9374 Scan engine 4.1.0.15 (corporate edition) and with a virus definition file Version 8/27/2003 rev. 21. No viruses were detected and AstraZeneca certifies that the enclosed CD-ROM is virus-free.

For your convenience we have also provided a brief Regulatory History and Organization review aid.

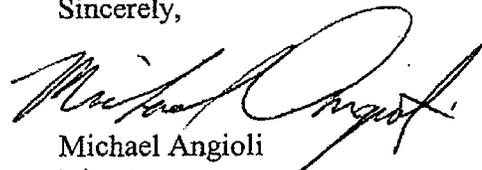
In accordance with 21 CFR 314.50 (l)(3), AstraZeneca is concurrently providing the FDA New England District Office with a field copy of this NDA.

As required in 21 CFR 54.4, certification (Form FDA 3454) forms are enclosed regarding the financial interests and arrangements for all of the clinical investigators who contributed to the covered clinical trials provided in this application. In addition, a certification statement is enclosed which states that AstraZeneca did not and will not use, in any capacity, the services of any person debarred under section 306(a) or (b).

In closing, this submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Please direct any questions or requests for additional information to me, or in my absence, to George A. Kummeth, Associate Director, at (302) 885-8415.

Sincerely,



Michael Angioli
Director
Regulatory Affairs
Telephone: (302) 885-1389
Fax: (302) 886-2822

Enclosure

cc

Cover Letter to:

Robert Justice, MD, MS, Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-180, Room 6B45
5600 Fishers Lane
Rockville, MD 20857

Cover Letter and Technical Review Copies to:

Melissa Furness, Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-180, Room 6B45
5600 Fishers Lane
Rockville, MD 20857

4 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 2

01/11/05

Office of Drug Safety

MEMO

To: Robert Justice, M.D.
Director, Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180)

From: Tina M. Tezky, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support (HFD-420)

Through: Alina R. Mahmud, R.Ph, M.S., Team Leader
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support (HFD-420)

CC: Melissa Furness
Project Manager, Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180)

Date: January 11, 2005

Re: DMETS Consult 03-0309-2; Nexium IV® (Esomeprazole for Injection) 20 mg and 40 mg; NDA #21-689

This memorandum is in response to a January 3, 2005 request from your Division for a final review of the proprietary name, Nexium IV. The proposed proprietary name was previously found acceptable by DMETS on February 17, 2004 (ODS consult 03-0309) and May 5, 2004 (ODS consult 03-0309-1). Revised container labels, carton and insert labeling were not provided for review and comment at this time.

Since the previous reviews, DMETS conducted a search of the FDA Adverse Event Reporting System (AERS) for all post-marketing safety reports of medication errors associated with Nexium. The search identified one potential complaint of possible confusion between the proprietary names Flexium and Nexium. Flexium is an herbal product promoted primarily for joint health. Both names share the same number of syllables (three). They also share the same ending ("exium") and differ in the initial letters ("N" vs. "F"); however, when scripted poorly there may be a resemblance between the "N" and "FI" (see writing sample below).

The image shows two lines of handwritten text. The first line is 'Flexium' and the second line is 'Nexium'. The 'N' in 'Nexium' is written in a way that makes it look like 'FI', illustrating the potential for confusion with 'Flexium'.

While the two names look and sound similar, there are several characteristics that help to differentiate the two products. Flexium is an over-the-counter herbal tablet containing SAM-e (S-adenosylmethionine 1,4-butanedisulfonate)/Glucosamine 200 mg/500 mg. Nexium IV is a single ingredient (esomeprazole) prescription product. The dosage strengths of the two products do not overlap. Nexium IV will be available in two different strengths (20 mg and 40 mg) and a differentiating strength would need to be identified prior to prescription filling. Likewise, the products differ in dosage form (tablets vs. injection) and indication for use (joint health vs. gastroesophageal reflux disease). Thus, even though the names do have look- and sound-alike similarities, DMETS believes that there are differences between the two products that will minimize the risk of confusion.

In summary, DMETS does not have any objections to the use of the proprietary name Nexium IV. Additionally, DDMAC finds the proprietary name Nexium IV acceptable from a promotional perspective. DMETS refers you to the label and labeling recommendations outlined in our February 17, 2004 review (ODS consult 03-0309). These recommendations were made in an effort to minimize potential user

error. DMETS considers this a final review. However, if approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

DMETS would appreciate feedback regarding the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Tina Tezky
1/27/05 03:53:24 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
1/28/05 08:14:32 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
1/28/05 03:56:26 PM
DRUG SAFETY OFFICE REVIEWER

REQUEST FOR CONSULTATION

TO (Division/Office):

**Jenise Toyer, HFD-420
Parklawn, Room 634**

FROM:

**Melissa Furness, HFD-180
Parklawn, 6B-45**

DATE January 03, 2005	IND NO.	NDA NO. 21-689	TYPE OF DOCUMENT	DATE OF DOCUMENT September 30, 2004
NAME OF DRUG Nexium (esomeprazole)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG PPI	DESIRED COMPLETION DATE March 15, 2005

NAME OF FIRM: **Astra Zenca**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY/EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|--|--|

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|--|

IV. DRUG EXPERIENCE

- | | |
|--|---|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|--|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS:

This is a second cycle resubmission for a type 3 New Drug Application. The PDUFA goal date is March 30, 2005. Please note that this application was submitted electronically, consequently, it may be found on the EDR (pathway – N21689 [September 30, 2004 AZ submission] - labeling folder). Also, please note that you have already completed two prior reviews regarding this proposed tradename date (ODS CONSULT #s: 03-0309 and 03-0309-1, respectively), but it is my understanding that you need to take another look at the proposed tradename 90 days prior to the PDUFA goal. Please let me know if you need any further information. Thanks in advance for your time and efforts! Melissa Furness – x77450.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> E-MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Melissa Furness
1/5/05 02:57:45 PM

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: NDA 21-689

Name of Drug: Nexium® I.V. (esomeprazole sodium) for Injection

Sponsor: Astra Zeneca

Date completed: 12/2003

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): electronic

Submission Date: 09/11/2003

Receipt Date: 09/12/2003

Filing Date: 11/10/2003

User-fee Goal Date(s): 07/12/2004

Proposed Indication: the short-term treatment (up to 10 days) of _____
_____ (GERD) as an alternative to oral therapy in patients when therapy
with Nexium Delayed-Release Capsules is not possible or appropriate.

Review

PART I: OVERALL FORMATTING^{a,d,e}

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	x		cover.pdf
2. Form FDA 356h (original signature)	x		356h.pdf
a. Establishment information	x		356h.pdf
b. Reference to DMF(s) & Other Applications	x		356h.pdf

3. User Fee FDA Form 3397	x		other\userfee.pdf
4. Patent information & certification	x		other\patinfo.pdf other\patcert.pdf
5. Debarment certification (Note: Must have a definitive statement)	x		other\estabdesc.pdf
6. Field Copy Certification	x		other\fieldcer.pdf
7. Financial Disclosure	x		other\finandis.pdf
8. Comprehensive Index	x		ndatoc.pdf
9. Pagination	x		
10. Summary Volume	x		Summary folder
11. Review Volumes	x		See different discipline folders
12. Labeling (PI, container, & carton labels)	x		Labeling folder
a. unannotated PI	x		Labeling folder
b. annotated PI	x		Labeling folder
c. immediate container	x		Labeling folder
d. carton	x		Labeling folder
e. patient package insert (PPI)		x	N/A
f. foreign labeling (English translation)		x	N/A
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	x		CRT folder
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	x		CRF folder

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY^{b,d,e}

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits			N/F
2. Foreign Marketing History	x		summary folder\foreignm.pdf
3. Summary of Each Technical Section	x		
a. Chemistry, Manufacturing, & Controls (CMC)	x		toc.pdf – cmc\cmctoc.pdf
b. Nonclinical Pharmacology/Toxicology	x		pharmtox folder
c. Human Pharmacokinetic & Bioavailability	x		hpbio folder
d. Microbiology	x		toc.pdf – cmc\cmctoc.pdf
e. Clinical Data & Results of Statistical Analysis	x		toc.pdf – clinstat\clintoc.pdf
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies		x	N/F
5. Summary of Safety	x		toc.pdf – summary\summarytoc.pdf- summary\clinsum.pdf
6. Summary of Efficacy	x		toc.pdf – summary\summarytoc.pdf- summary\clinsum.pdf

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS^{c,d,e}

	Y	N	COMMENTS (If paper: list volume & page numbers)

			(If electronic: list folder & page numbers)
1. List of Investigators	x		clinstat folder\invest.pdf
2. Controlled Clinical Studies	x		clinstat folder
a. Table of all studies	x		clinstat folder\tabstudy.pdf
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	x		clinstat folder
c. Optional overall summary & evaluation of data from controlled clinical studies		x	N/F
3. Integrated Summary of Efficacy (ISE)	x		summary folder\clinsum.pdf
4. Integrated Summary of Safety (ISS)	x		summary folder\clinsum.pdf
5. Drug Abuse & Overdosage Information		x	N/F
6. Integrated Summary of Benefits & Risks of the Drug		x	N/F
7. Gender/Race/Age Safety & Efficacy Analysis of Studies		x	N/F

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS^{d,e}

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population	x		Other\pedwaiv.pdf
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)		x	N/A as e-submission
a. Proposed unannotated labeling in MS WORD	x		Labeling folder
b. Stability data in SAS data set format (only if paper submission)		x	N/A as e-submission
c. Efficacy data in SAS data set format (only if paper submission)		x	N/A as e-submission
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		x	N/A as e-submission
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		x	N/A as e-submission
3. Exclusivity Statement (optional)	x		Other\exclusiv.pdf

Y=Yes (Present), N=No (Absent)

Melissa Hancock Furness
Regulatory Project Manager
12/2003

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/s/

Melissa Furness
6/28/04 08:20:09 AM
CSO

Melissa Furness
6/28/04 08:23:24 AM
CSO

06/24/04

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications



Memorandum

Pre-Decisional Agency Information

Date: June 24, 2004

To: **Melissa Furness**
Project Manager,
Division of Gastrointestinal and Coagulation Drug Products

From: **Elaine J. Hu**, Regulatory Review Officer
Shannon Benedetto, Regulatory Review Officer

Subject: **NDA 21-689**
DDMAC Labeling comments for Nexium I.V. (esomeprazole sodium)

DDMAC has reviewed the proposed labeling and offers the following comments:

CLINICAL STUDIES: Acid Suppression in Gastroesophageal Reflux Disease (GERD)

The proposed Nexium I.V. label states the following:



Are these statements necessary here? Similar detail is not included in the Protonix I.V. PI. In addition, the phrase, _____ is promotional in tone.

CLINICAL STUDIES: Safety Study in Patients With Erosive Esophagitis

This section of the proposed Nexium I.V. PI discusses secondary endpoints including

_____ The treatment included one-week treatment with Nexium I.V. 40 mg followed by an open treatment period with all subjects taking oral Nexium 40 mg for three weeks. In addition, the proposed section states, _____

Is there substantial evidence to support that Nexium I.V. is effective in a treatment regimen to _____? As this section of the proposed PI is currently worded, the sponsor may make promotional claims of Nexium I.V. in a treatment regimen to _____. Therefore, if Nexium I.V. is *not* indicated specifically in a treatment regimen to _____ we recommend deletion all mention of _____ in the proposed Nexium I.V. PI, as well as deletion of the statement: _____

INDICATIONS AND USAGE

1. The proposed label includes the following indication:

Nexium I.V. for Injection is indicated for the short-term treatment (up to 10 days) of _____ (GERD) as an alternative therapy with NEXIUM Delayed Release Capsules is not possible or appropriate.

- 2.

The Prevacid IV label also includes a similar statement.

ADVERSE REACTIONS: Safety Experience with Intravenous NEXIUM

1. The proposed labeling includes the following information about adverse reactions:

Adverse experiences occurring in >1% of patients treated with intravenous esomeprazole (n=359) in trials irrespective of the relationship to NEXIUM are listed below by body system:

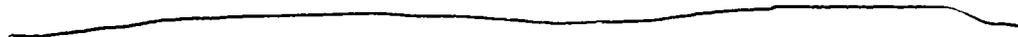
Skin and appendages disorders: pruritis; **Central and peripheral nervous system disorders:** dizziness, headache; **Gastrointestinal system disorders:** abdominal pain, constipation, diarrhea, dyspepsia, flatulence, mouth dry, nausea; **Respiratory system disorders:** respiratory infection, sinusitis; **Body as a whole – general disorders:**

*AE associated with test procedure and **Application site disorders:**
application site reaction.*

- 
- Please consider presenting the incidences (i.e., percentages) of each adverse event rather than just a list.

ADVERSE REACTIONS: Safety Experience with oral NEXIUM

1. The proposed label includes the following statement:



Although other labels have used  we recommend deletion of this term as it is promotional in tone.

- 2.

3. We suggest deletion of the entire section of "Additional adverse events that were reported as possibly or probably related to NEXIUM with an incidence <1%" given on pages 13-14. The CDER draft guidance on the adverse reactions section of labeling discourages the use of exhaustive lists of such events.

DOSAGE AND ADMINISTRATION

- 1.





2. Should a statement be included here about switching to oral esomeprazole, as stated in the "INDICATIONS AND USAGE" section? For example, the Protonix I.V. PI states the following in the "DOSAGE AND ADMINISTRATION" section: "Treatment with PROTONIX I.V. for Injection should be discontinued as soon as the patient is able to resume treatment with PROTONIX Delayed-Release Tablets." The Prevacid IV label also includes a similar statement.

3. This section states, _____ Is there evidence to support Nexium I.V.'s use as _____ This should also be clarified in the "INDICATIONS AND USAGE" section of the proposed PI.
4. Should a statement be included here about the length of treatment with Nexium I.V. (i.e., not more than 10 days)? For example, the Protonix IV label includes the following statement:

Safety and efficacy of PROTONIX I.V. for Injection as a treatment of _____ GERD _____ for more than 10 days have not been demonstrated (see INDICATIONS AND USAGE).

The Prevacid IV label also includes a similar statement.

Thank you for this opportunity to provide comments. If you have any questions, please contact Elaine Hu at 301-827-3888 or HUE@CDER.FDA.GOV.

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/s/

Elaine J. Hu
6/24/04 04:03:43 PM
DDMAC REVIEWER

Attachment 1



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: 04/23/04

To: George Kummeth	From: Melissa Hancock Furness
Company: Astra-Zeneca	
Fax number: 302-886-2822	Fax number: 301-443-9285
Phone number: 302-885-8415	Phone number: 301-827-7450
Subject: NDA 21-689 – 02/01/04 Meeting Request - Responses to the questions submitted in your 03/30/04 Meeting Background Package	

Total no. of pages including cover:

Comments: Attached are the FDA answers to your questions. You have the option of canceling our meeting of April 28, 2004 if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible whether you are canceling the meeting.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-7450. Thank you.

Please find below our response to the question submitted in your **March 30, 2004 Meeting Background Package**. Our responses are in **bold**.

Question 1

AstraZeneca has summarized the compatibility testing undertaken for submission of NDA 21-689, and has proposed additional compatibility testing. Does the Agency concur with the proposed test protocol (including test parameters) for additional compatibility studies with the Nexium IV drug product?

Response: No (see response below).

Question 2

Lactated Ringer's Injection and 5% Dextrose Injection are not recommended as diluents for Nexium IV since our test results have demonstrated that the drug product reconstituted in these diluents is less chemically stable (the levels of degradants are higher) compared with drug product reconstituted in 0.9% sodium chloride solution. Further, Lactated Ringer's Injection, USP is not currently available in a 50 ml package, which is the required volume of diluent for the infusion dosing. Therefore, AstraZeneca proposes no further compatibility testing of Nexium IV reconstituted in these solutions.

Does the Agency concur that as 5% Dextrose Injection and Lactated Ringer's Injection will not be approved diluents for reconstituting Nexium IV (for reasons stated), sufficient compatibility testing has been conducted and no further compatibility testing with these diluents is necessary?

Response: You state that Lactated Ringer's Injection and Dextrose Injection are not recommended as diluents because the reconstituted drug product is less stable in these diluents. Please provide data regarding the level of degradants at different time points, for example, 1 hour, 2 hours, 4 hours, 12 hours, 24 hours, ect., to support this statement. If the data confirms that Nexium IV is chemically unstable in Lactated Ringer's Injection and Dextrose Injection then further testing with these diluents is not required and the drug will need to be appropriately labeled in accordance with this data. In addition, we would like to remind you to conduct additional compatibility studies using IV bags of all commercial compositions (e.g. PVC, Polyolefin, etc.). These studies should include the tubing, connectors, syringes, etc. supplied by different manufacturers and using saline as your diluent.

Question 3

Has the Agency identified any additional review issues and/or deficiencies related to the data included in NDA 21-689 which can be communicated at this time?

Response: The application is still under review. We will let you know at a later date if we identify any further issues.

Additional Comments:

Please provide your post-marketing safety regarding your use of Nexium IV in other countries.

Attachment 2

MEMORANDUM OF TELECONFERENCE MINUTES

Meeting Date: April 28, 2004

Time: 2:30 PM - 4:00 PM

Application: NDA 21-689
NEXIUM®IV (esomeprazole sodium) for Injection

Sponsor: AstraZeneca LP

Type of Meeting: Type C Meeting

Meeting Chair: Eric Duffy, Ph.D.

Meeting Recorder: Melissa Furness, B.S.

FDA Attendees:

Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180)

Joyce Korvick, M.D., M.P.H., Deputy Director
Hugo Gallo-Torres, M.D., Ph.D., Medical Team Leader, GI Drugs
Gail Moreschi, M.D., M.P.H., Medical Officer
Melissa Furness, B.S., Project Manager

Division of New Drug Chemistry II (HFD-820)

Eric Duffy, Ph.D., Director, New Drug Chemistry II

Division of New Drug Chemistry II (HFD-180)

Liang Zhou, Ph.D., Chemistry Team Leader
Ali Al Hakim Ph.D., Chemistry Reviewer

Sponsor Attendees:

AstraZeneca LP-US

Barry Sickels, M.S., Executive Director, Regulatory Affairs
George Kummeth, MBA, Director, Regulatory Affairs
Carol Stinson-Fisher, Associate Director, Technical Regulatory Affairs
Miraliakbari, Pharm. D., Regulatory Project Manager, Regulatory Affairs
Samuel Herald, Regulatory Project Associate, Regulatory Affairs

AstraZeneca LP-Sweden

Per Niklasson, Regulatory Affairs Director, Reg CMC
Anna Bergendal, Associate Director, Pharmaceutical Project Manager
Mikael Brülls, Manager, Product Development
Svante Johansson, Senior Scientist, Analytical Development, Product Analysis II

Background: On March 30, 2004 AstraZeneca LP submitted a background package containing Chemistry, Manufacturing and Control (CMC) information and questions in connection with the NDA submission of NEXIUM® I.V. (esomeprazole sodium) for Injection. On April 23, 2004 FDA provided responses to the questions from our CMC background package.

Meeting Objectives: To discuss the “potential review issues” identified in the November 20, 2003 Filing Communication letter and reach agreement on the optimal approach for designing the compatibility protocol and choosing combinations of infusion devices and diluents.

Question 1

AstraZeneca has summarized the compatibility testing undertaken for submission of NDA 21-689, and has proposed additional compatibility testing. Does the Agency concur with the proposed test protocol (including test parameters) for additional compatibility studies with the Nexium IV drug product?

Response: No (see response below).

Discussion:

The Sponsor summarized Tables 1, 2, 3, 4 and 6 from the March 30 background package and requested further clarification on the acceptability of the proposed testing protocol for saline.

The Agency indicated that the chosen IV bags, tubing, connectors and syringes for saline are considered representative of commercial compositions and representative regarding different manufacturers. The Agency requested that the compositions of IV saline bags listed in or Table 1 from the March 30 background package (PVC, polypropylene and polyethylene, and polypropylene and polyamide) be tested with all infusion and extension sets listed in the compatibility protocol. These saline bags and various infusion components will be tested at 0, 6, 12 and 24 hours. The test results from these additional studies must be submitted to the NDA.

The Sponsor agreed to perform this additional testing and will notify the Agency of the anticipated timing for submission of the data.

The Sponsor stated that results from particulate testing using saline and preliminary data from studies employing combinations of the proposed diluent and plastic components indicate that subvisible particles remain within USP limits and that no requirement for use of an _____ for our drug product would be necessary. The Agency replied that the necessity of an _____ depended upon their final review of all compatibility test data, including the additional testing noted above. The Sponsor reiterated that this is understood but wanted to gain agreement with the principle that if particulate results remained within USP limits, then no _____ would be necessary for saline. The Agency replied that they agreed with this principle.

Question 2

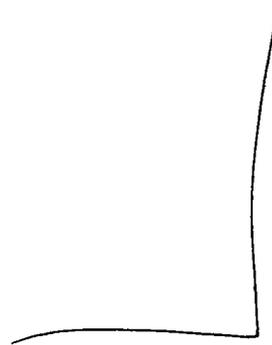
Lactated Ringer's Injection and 5% Dextrose Injection are not recommended as diluents for Nexium IV since our test results have demonstrated that the drug product reconstituted in these diluents is less chemically stable (the levels of degradants are higher) compared with drug product reconstituted in 0.9% sodium chloride solution. Further, Lactated Ringer's Injection, USP is not currently available in a 50 ml package, which is the required volume of diluent for the infusion dosing. Therefore, AstraZeneca proposes no further compatibility testing of Nexium IV reconstituted in these solutions.

Does the Agency concur that as 5% Dextrose Injection and Lactated Ringer's Injection will not be approved diluents for reconstituting Nexium IV (for reasons stated), sufficient compatibility testing has been conducted and no further compatibility testing with these diluents is necessary?

Response: You state that Lactated Ringer's Injection and Dextrose Injection are not recommended as diluents because the reconstituted drug product is less stable in these diluents. Please provide data regarding the level of degradants at different time points, for example, 1 hour, 2 hours, 4 hours, 12 hours, 24 hours, etc., to support this statement. If the data confirms that Nexium IV is chemically unstable in Lactated Ringer's Injection and Dextrose Injection then further testing with these diluents is not required and the drug will need to be appropriately labeled in accordance with this data. In addition, we would like to remind you to conduct compatibility studies using IV bags of all commercial compositions (e.g. PVC, Polyolefin, etc.). These studies should include the tubing, connectors, syringes, etc. supplied by different manufacturers and using saline as your diluent.

Discussion:





Question 3

Has the Agency identified any additional review issues and /or deficiencies related to the data included in NDA 21-689 which can be communicated at this time?

Response: The application is still under review. We will let you know at a later date if we identify any further issues.

Additional Comments:

Please provide your post-marketing safety regarding your use of Nexium IV in other countries.

Discussion:

The Agency indicated that the application is still under review, but requested post-marketing information from other countries in which this product is approved.

The Sponsor indicated that they were collecting the requested information, and that it will be submitted to the Agency by mid-May in the Nexium Annual Periodic Safety Update Report (PSUR).

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/s/

Melissa Furness
5/26/04 11:43:09 AM

05/06/04

Office of Drug Safety

MEMO

To: Robert Justice, MD
Director, Division of Gastro-Intestinal and Coagulation Drug Products, HFD-180

From: Denise P. Toyer, PharmD
Team Leader, Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

Through: Carol A. Holquist, R.Ph.
Director, Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

CC: Melissa Furness
Project Manager, Division of Gastro-Intestinal and Coagulation Drug Products, HFD-180

Date: May 5, 2004

Re: ODS Consult 03-0309-1, Nexium IV (Esomeprazole for Injection) 20 mg and 40 mg;
NDA 21-689

This memorandum is in response to an April 21, 2004 request from your Division for a final review of the proprietary name, Nexium IV. Revised container labels, carton and insert labeling were not provided for review and comment.

DMETS has not identified any additional proprietary names as having potential sound-alike and look-alike confusion with Nexium IV since we conducted our initial review dated February 17, 2004 that would render the name objectionable (see ODS Consult 03-0309).

In summary, DMETS does not have any objections to the use of the proprietary name Nexium IV. Additionally, DDMAC finds the proprietary name Nexium IV acceptable from a promotional perspective. DMETS reminds you of our label and labeling recommendations outlined in our February 17, 2004 review. These recommendations were made in an effort to minimize potential user error. DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

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/s/

Denise Toyer
5/6/04 04:01:10 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/6/04 04:15:14 PM
DRUG SAFETY OFFICE REVIEWER

05/04/04



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: 05/04/2004

To: George Kummeth	From: Melissa Hancock Furness
Company: Astra-Zeneca	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 302-886-2822	Fax number: 301-443-9285
Phone number: 302-885-8415	Phone number: 301-827-7450

Subject: NDA 21-689 - Response to 04/28/04 E-mail

Total no. of pages including cover: 4

Comments:

Please find attached our response (see Attachment 2) to your 04/28/04 (see Attachment 1) e-mail.

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-689

Astra Zeneca LP
Attention: George Kummeth, Director Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Kummeth:

We refer to your February 10, 2004, correspondence (received February 11, 2004) requesting a meeting to discuss the Agency's November 11, 2003 Filing Communication letter.

We further refer to our correspondences sent to you by facsimile on April 23, 2004 (see attachment 1) which contained our responses to the questions submitted in your March 30, 2004 meeting background package.

In addition, please refer to the meeting between representatives of your firm and FDA on April 28, 2004 (see attachment 2). The purpose of the meeting was to continue discussion and to provide clarification regarding The Agency's November 11, 2003 Filing Communication letter regarding NDA 21-689, Nexium IV.

Therefore, the attached responses, sent to you by facsimile April 23, 2004 and the minutes of the meeting held on April 28, 2004, represent the official minutes of the scheduled meeting. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 827-7450.

Sincerely,

{See appended electronic signature page}

Melissa Hancock Furness
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachments:

Attachment 1

-----Original Message-----

From: Kummeth, George [mailto:George.Kummeth@astrazeneca.com]

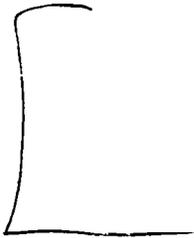
Sent: Thursday, April 29, 2004 2:35 PM

To: 'Furness, Melissa'

Subject: NDA 21-689, Nexium IV, April 28, 2004 FDA Meeting

Hello Melissa,

With reference to yesterday's teleconference on Nexium IV, I am providing follow-up information on the availability of Lactated Ringer's Injection in a 50 ml bag.



If possible to communicate, we would appreciate further advice from the Agency regarding the commercial availability of Lactated Ringer's in a 50 ml bag (supplier, item number, etc.). Additionally, if a 50 ml bag is not commercially available, we would appreciate guidance on the conduct of our Nexium IV compatibility studies using Lactated Ringer's.

Thank you and regards,

George

George Kummeth
Director, Regulatory Affairs
(tele) 302-885-8415

Attachment 2

Regarding the Lactated Ringer's bags, it is true that the only bag available is 250 mL. Please perform your compatibility studies using 250 mL and 5 vials of the drug product.

Your proposal regarding _____

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/s/

Melissa Furness
5/4/04 03:45:52 PM
CSO

Melissa Furness
5/4/04 03:46:50 PM
CSO

02/17/04

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED:

November 28, 2003

DESIRED COMPLETION DATE:

January 28, 2004

ODS CONSULT #: 03-0309**PDUFA DATE:** July 10, 2004

TO: Robert Justice, M.D.
 Director, Division of Gastro-Intestinal and Coagulation Drug Products
 HFD-180

THROUGH: Melissa Furness
 Project Manager
 HFD-180

PRODUCT NAME:

Nexium I.V.
 (Esomeprazole Sodium for Injection)
 20 mg and 40 mg

NDA SPONSOR: Astra-Zeneca LP**NDA #:** 21-689**SAFETY EVALUATOR:** Linda M. Wisniewski, RN**RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name, Nexium I.V. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Nexium I.V. acceptable from a promotional perspective.

Carol Holquist, RPh
 Deputy Director,
 Division of Medication Errors and Technical Support
 Office of Drug Safety
 Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, RPh
 Associate Director
 Office of Drug Safety
 Center for Drug Evaluation and Research
 Food and Drug Administration

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Nexium I.V. to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (both inpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Nexium IV. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Nexium I.V. acceptable from a promotional perspective.
2. The Expert Panel identified one proprietary name as having the potential for confusion with Nexium I.V. The product is listed in table 1 (see below), along with the dosage forms available and usual dosage.
3. DMETS also had concerns that the modifier 'I.V.' could be misinterpreted as representing the Roman numeral IV.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Nexium I.V.	For injection: 20 mg and 40 mg	20 mg or 40 mg daily	N/A
Nexium	Esomeprazole Magnesium Delayed-Release capsule 20 mg 40 mg	20 mg or 40 mg daily	SA/LA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

¹ MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic and orthographic similarities to Nexium I.V. were discussed by the Expert Panel (EPD).

C. ADVERSE EVENT REPORTING SYSTEM (AERS)

Nexium has been marketed since February 2001 therefore DMETS conducted a search of the FDA Adverse Event Reporting System (AERS) for all post-marketing safety reports of medication errors associated with Nexium. The MEDDRA Preferred Terms (PT) “Medication Error”, “accidental overdose”, and “overdose nos” and the terms “Nexium”, “Esomeprazole”, “Nex%”, and “Esomep%” were used as search criteria. The search identified ten cases. However, only one case involved confusion between Nexium and another proprietary name, Neurontin. Due to lack of further information in the case, it is difficult to determine causality.

Additionally, the electronic Orange Book and the Saegis Pharma-in Use⁶ databases were searched for all approved products that employ the modifier “I.V.” in the proprietary name. This search yielded the following products: Feridex I.V., Indocin I.V., Merrem I.V., and Flagyl I.V., Protonix I.V., Metro I.V., Bactrim I.V., and Septra IV. The AERS database was searched to determine if the “I.V.” modifier had any impact on the occurrence of medication errors. This search was conducted using the Preferred Terms (PT) “Medication Error”, “accidental overdose” and “overdose nos” and the proprietary and established names of each of the aforementioned products. The AERS searches resulted in a total of 406 reports: Feridex I.V. (1 report), Indocin I.V. (4 reports), Merrem I.V. (3 reports), Flagyl I.V. (87 reports), Protonix (48 reports), Metro I.V. (92 reports), Bactrim (90 reports), and Septra (82 reports). However, none of the reports indicated that the modifier ‘I.V.’ had impact on any of the errors.

D. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Nexium I.V. with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Two inpatient orders consisting of a combination of marketed and unapproved drug products and a prescription for Nexium I.V. (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, a verbal order was recorded on voice mail. The voice mail message was then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders,

⁶ Data provided by Thomson & Thomson’s SAEGIS™ Online Service, available at www.thomson-thomson.com

the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Inpatient RX # 1: <i>Increase Nexium I.V. to 40mg daily over 30 minutes</i>	Increase Nexium I.V. to 40 mg daily over 30 minutes.
Inpatient RX # 2: <i>Increase Nexium IV. to 40mg daily over 30min</i>	

2. Results:

The prescription studies results show that 34 (approximately 50%) of the participants responded with the root name “Nexium” without the modifier, which represents the oral formulation of the product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Nexium I.V., the primary concerns related to look-alike and sound-alike confusion with Nexium capsules. Safety concerns related to the I.V. modifier were also considered.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Nexium I.V. could be confused with Nexium. Thirty-four respondents from the Nexium I.V. study omitted the modifier ‘I.V.’

1. Look-alike and Sound-alike concerns:

DMETS did not identify any other look-alike or sound-alike names that might be confused with Nexium I.V. other than the product Nexium (capsules). Since both products share the root name (Nexium) there was concern that confusion might occur between these two products if the modifier were omitted. This potential confusion was confirmed in the prescription studies conducted by DMETS. However, the risk of confusion is minimal given the products contain the same active ingredient.

2. Concern with “I.V.” portion of Nexium I.V.

- a. There is potential for the modifier “I.V.” to be omitted from written or verbal orders for Nexium IV. DMETS believes that this does not create the potential for confusion, because the modifier “I.V.” is also the route of administration. The FDA generally does not encourage the route of administration in the proprietary name. However, several products are currently marketed with this modifier and no errors have occurred with its use. If the modifier were omitted, the route of administration would have to be included in the scripted order, thereby requiring the administrator of the medication to use the appropriate form.

- b. DMETS also identified a concern that the 'I.V' portion of the proposed name could be misinterpreted in this context as the Roman numeral four. However, an AERS search for medication errors associated with "I.V." in the proprietary name yielded no relevant reports of this type of confusion

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Nexium I.V., DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

- 1. Include the route of administration _____ on the principal display panel.
- 2. Revise the strength to read _____

B. CONTAINER LABEL

- 1. See General Comments.
- 2. 
- 3. 
- 4. _____

C. CARTON LABELING (10 vials)

- 1. See General Comments.
- 2. 
- 3. _____

- 4. _____

D. INSERT LABELING

1. GENERAL COMMENT

When referring to the product strength or dosing recommendations; whole numbers should be expressed without a trailing zero (e.g., 5 mL rather than 5.0 mL). Revise accordingly throughout the text of the insert.

1 Page(s) Withheld

 Trade Secret / Confidential

 X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 1A

IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name Nexium I.V. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name Nexium I.V. acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Linda M. Wisniewski, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise P. Toyer, PharmD.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A: NDA 21-689 NEXIUM I.V.

ODS Consult: 03-0309

Written Inpatient #1	Written Inpatient #2	Verbal Outpatient
Neravin	Nexium	Maxium IV
Nexim	Nexium	Nexium
Nexim IV	Nexium	Nexium
Nexium	Nexium	Nexium
Nexium I.V	nexium	Nexium
Nexium i.v.	nexium	Nexium
Nexium I.V.	Nexium	Nexium
Nexium I.V.	Nexium	Nexium
Nexium IV	Nexium	Nexium
Nexium iv	Nexium IV	Nexium
Nexium IV	nexium iv	Nexium IV
Nexium IV	Nexium IV	Nexium IV
Nexium IV	Nexium IV	Nexium iv
Nexium IV	Nexium IV	Nexium IV
Nexium IV	Nexium IV	Nexium IV
Nexium IV	Nexium iv	Nexium IV
Nexium IV	Nexium IV	Nexium IV
rextrim IV	Nexium IV	Nexium IV
	Nexium IV	Nexium IV
		Nexium IV
		Tenexium iv

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/s/

Linda Wisniewski
2/17/04 10:34:07 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/17/04 12:38:09 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/17/04 02:40:47 PM
DRUG SAFETY OFFICE REVIEWER

04/23/04



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: 04/23/04

To: George Kummeth	From: Melissa Hancock Furness
Company: Astra-Zeneca	
Fax number: 302-886-2822	Fax number: 301-443-9285
Phone number: 302-885-8415	Phone number: 301-827-7450
Subject: NDA 21-689 – 02/01/04 Meeting Request - Responses to the questions submitted in your 03/30/04 Meeting Background Package	

Total no. of pages including cover:

Comments: Attached are the FDA answers to your questions. You have the option of canceling our meeting of April 28, 2004 if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible whether you are canceling the meeting.

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Please find below our response to the question submitted in your **March 30, 2004 Meeting Background Package**. Our responses are in **bold**.

Question 1

AstraZeneca has summarized the compatibility testing undertaken for submission of NDA 21-689, and has proposed additional compatibility testing. Does the Agency concur with the proposed test protocol (including test parameters) for additional compatibility studies with the Nexium IV drug product?

Response: No (see response below).

Question 2

Lactated Ringer's Injection and 5% Dextrose Injection are not recommended as diluents for Nexium IV since our test results have demonstrated that the drug product reconstituted in these diluents is less chemically stable (the levels of degradants are higher) compared with drug product reconstituted in 0.9% sodium chloride solution. Further, Lactated Ringer's Injection, USP is not currently available in a 50 ml package, which is the required volume of diluent for the infusion dosing. Therefore, AstraZeneca proposes no further compatibility testing of Nexium IV reconstituted in these solutions.

Does the Agency concur that as 5% Dextrose Injection and Lactated Ringer's Injection will not be approved diluents for reconstituting Nexium IV (for reasons stated), sufficient compatibility testing has been conducted and no further compatibility testing with these diluents is necessary?

Response: You state that Lactated Ringer's Injection and Dextrose Injection are not recommended as diluents because the reconstituted drug product is less stable in these diluents. Please provide data regarding the level of degradants at different time points, for example, 1 hour, 2 hours, 4 hours, 12 hours, 24 hours, ect., to support this statement. If the data confirms that Nexium IV is chemically unstable in Lactated Ringer's Injection and Dextrose Injection then further testing with these diluents is not required and the drug will need to be appropriately labeled in accordance with this data. In addition, we would like to remind you to conduct additional compatibility studies using IV bags of all commercial compositions (e.g. PVC, Polyolefin, etc.). These studies should include the tubing, connectors, syringes, etc. supplied by different manufacturers and using saline as your diluent.

Question 3

Has the Agency identified any additional review issues and/or deficiencies related to the data included in NDA 21-689 which can be communicated at this time?

Response: The application is still under review. We will let you know at a later date if we identify any further issues.

Additional Comments:

Please provide your post-marketing safety regarding your use of Nexium IV in other countries.

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/s/

Melissa Furness
4/23/04 03:22:44 PM
CSO

04/22/04

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Jerry Philips, HFD-400 Parklawn 15B-23		FROM: Melissa Furness, HFD-180 Parklawn 6B-45		
DATE April 21, 2004	IND NO.	NDA NO. 21-689	TYPE OF DOCUMENT	DATE OF DOCUMENT September 10, 2004
NAME OF DRUG		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE June 30, 2004
NAME OF FIRM:				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY				
<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT				
<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: This is a type 3 New Drug Application. The PDUFA goal date is 07/10/04. Please note that this application was submitted electronically, consequently, it may be found on the EDR (pathway – N21689/labeling folder). Also, please note that you have already completed your review of this Tradename, but you asked that I submit another consult for you to take another look at the Tradename 90 days prior to the PDUFA goal date (ODS CONSULT #: 03-0309). Thanks much! Melissa Furness – x77450.				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Melissa Furness
4/22/04 09:43:39 AM

02/23/04



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: 02/23/04

To: George Kummeth	From: Melissa Hancock Furness
Company: Astra-Zeneca	
Fax number: 302-886-2822	Fax number: 301-443-9285
Phone number: 302-885-8415	Phone number: 301-827-7450
Subject: Meeting Confirmation – NDA 21-689 (Nexium IV) – 02/10/04 Meeting Request	

Total no. of pages including cover: 2

Comments:

This will confirm the meeting between Astra-Zeneca and the FDA to be held on **April 28, 2004, 2:30 – 4:00 PM**. I am also attaching a tentative list of attendees from the FDA who will be attending this meeting.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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The following is a tentative list of FDA participants:

Dr. Robert Justice, Director, DGCDP

Dr. Joyce Korvick, Deputy Director, DGCDP

Dr. Hugo Gallo-Torres, Medical Team Leader

Dr. Gail Moreschi, Medical Reviewer

Dr. Liang Zhou, Chemistry Team Leader

Dr. Ali Al-Hakim, Chemistry Reviewer

Dr. Suresh Doddapaneni, Biopharmaceutics Team Leader

Dr. Suliman Al-Fayoumi, Biopharmaceutics Reviewer

Dr. Jasti Choudary, Supervisory Pharmacologist

Dr. Yash Chopra, Pharmacology Reviewer

Ms. Melissa Furness, Regulatory Project Manager

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/s/

Melissa Furness
2/23/04 01:00:59 PM

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/s/

Melissa Furness
11/26/03 09:28:39 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-689

AstraZeneca LP
Attention: George Kummeth
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Kummeth:

Please refer to your September 10, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexium[®] I.V. (esomeprazole magnesium) for Injection.

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 November 10, 2003 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. Please provide additional statistical information described below
2. Conduct additional compatibility studies using IV bags of all commercial compositions (e.g. PVC, Polyolefin, etc.). These studies should include the tubing, connectors, syringes, etc. supplied by different manufacturers and commonly used diluents (e.g. Lactated Ringer's Injection, 5% Dextrose Injection, etc.) even if they are not identified in the proposed drug product labeling. The studies should include testing for potency (assay), pH, impurities and — particulates at different time point within 24 hours.

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.

We request that you submit the following:

1. Please provide the following information for Study SH-NEP-0006:
 - a) Please provide the requested information in electronic format consistent with the guidance, *Regulatory Submissions in Electronic Format; General Considerations*. Please

include the following variables:

- Study number (or Protocol number);
- Investigator or Center code;
- Patient number/name;
- Treatment name;
- Intent-to-Treat/Safety population (yes or no);
- Per-Protocol Patient population (yes or no);
- Gender;
- Age;
- Race;
- Height;
- Weight;
- Baseline LA classification;
- Healing after four-week treatment of erosive reflux esophagitis (yes or no).

b) 



2. Upon completion, please submit the results from the requested compatibility studies.

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, call Melissa Hancock Furness, Regulatory Project Manager, at (301) 827-7450.

Sincerely,

{See appended electronic signature page}

Brian Strongin R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastrointestinal & Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
11/20/03 04:24:34 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-689

AstraZeneca LP
Attention: George Kummeth
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Kummeth:

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: Nexium[®] I.V. (esomeprazole magnesium) for Injection

Review Priority Classification: Standard (S)

Date of Application: September 10, 2003

Date of Receipt: September 10, 2003

Our Reference Number: NDA 21-689

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 November 10, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 10, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-689

Page 2

If you have any questions, call me at (301) 827-7450.

Sincerely,

{See appended electronic signature page}

Melissa Hancock Furness
Regulatory Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Melissa Furness
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