

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206940Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

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

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and Composition)
and/or Method of Use*

NDA NUMBER

206940

NAME OF APPLICANT/NDA HOLDER

Furiex Pharmaceuticals, Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)

(b) (4)

ACTIVE INGREDIENT(S)

eluxadoline

STRENGTH(S)

75 mg

100 mg

DOSAGE FORM

75 and 100-mg tablets

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

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

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

FDA will not list patent information if you submit 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

8,344,011

b. Issue Date of Patent

January 1, 2013

c. Expiration Date of Patent

March 14, 2025

d. Name of Patent Owner

Janssen Pharmaceutica, N.V.

Address (of Patent Owner)

Turnhoutseweg 30

City/State

2340 Beerse

ZIP Code

Belgium

FAX Number (if available)

32 2 749 2558

Telephone Number

32 14 60 21 11

E-Mail Address (if available)

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

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

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

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

Yes

No

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

Yes

No

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

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> 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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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).	<input type="checkbox"/> Yes	<input type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
1-78	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> 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 proposed labeling.) XENRYMA (eluxadoline) is indicated for the treatment of diarrhea and abdominal pain in men and women with diarrhea predominant irritable bowel syndrome. The patent claims cover the use of eluxadoline to treat the gastrointestinal disorder diarrhea predominant irritable bowel syndrome, or to treat pain.	

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.	<input type="checkbox"/> 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

Gail M. FE

20 May 2014

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 314.63(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Gail McIntyre	
Address 3900 Paramount Parkway, Suite 150	City/State Morrisville, NC
ZIP Code 27560	Telephone Number 919-456-7800
FAX Number (if available) 919-456-7850	E-Mail Address (if available) gail.mcintyre@furiex.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

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

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7620 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

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

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

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

2. Drug Substance (Active Ingredient)

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

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

3. Drug Product (Composition/Formulation)

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

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

4. Method of Use

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

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Identify the precise words of the approval labeling that describe with specificity the patented method of use.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

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

**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

206940

NAME OF APPLICANT/NDA HOLDER

Furiex Pharmaceuticals, Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)

XENRYMA

ACTIVE INGREDIENT(S)

eluxadoline

STRENGTH(S)

75 mg
100 mg

DOSAGE FORM

75 and 100-mg tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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FDA will not list patent information if you submit 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

7,786,158

b. Issue Date of Patent

August 31, 2010

c. Expiration Date of Patent

March 14, 2025

d. Name of Patent Owner

Janssen Pharmaceutica, N.V.

Address (of Patent Owner)

Turnhoutseweg 30

City/State

2340 Beerse

ZIP Code

Belgium

FAX Number (if available)

32 2 749 2558

Telephone Number

32 14 60 21 11

E-Mail Address (if available)

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

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

City/State

ZIP Code

Telephone Number

FAX Number (if available)

E-Mail Address (if available)

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

Yes

No

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

Yes

No

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

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) (as listed in the patent) Does (Do) the patent claim(s) 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 proposed 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

Gail McIntyre

20 May 2014

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.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Gail McIntyre	
Address 3900 Paramount Parkway, Suite 150	City/State Morrisville, NC
ZIP Code 27560	Telephone Number 919-456-7800
FAX Number (if available) 919-456-7850	E-Mail Address (if available) gail.mcintyre@furiex.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

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

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7620 Standish Place, Rockville, MD 20855.
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First Section

Complete all items in this section.

1. General Section

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

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

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

2. Drug Substance (Active Ingredient)

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

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

3. Drug Product (Composition/Formulation)

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

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

4. Method of Use

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

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Identify the precise words of the approval labeling that describe with specificity the patented method of use.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

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

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

*For Each Patent That Claims a Drug Substance
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Furiex Pharmaceuticals, Inc.

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XENRYMA

ACTIVE INGREDIENT(S)

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75 and 100-mg tablets

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FDA will not list patent information if you submit 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

7,741,356

b. Issue Date of Patent

June 22, 2010

c. Expiration Date of Patent

March 25, 2028

d. Name of Patent Owner

Janssen Pharmaceutica, N.V.

Address (of Patent Owner)

Turnhoutseweg 30

City/State

2340 Beerse

ZIP Code

Belgium

FAX Number (if available)

32 2 749 2558

Telephone Number

32 14 60 21 11

E-Mail Address (if available)

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

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

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

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

Yes

No

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

Yes

No

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

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) (as listed in the patent) Does (Do) the patent claim(s) 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 proposed 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

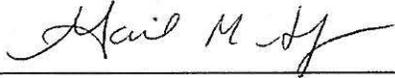
6. Declaration Certification

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



20 May 2014

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.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Gail McIntyre	
Address 3900 Paramount Parkway, Suite 150	City/State Morrisville, NC
ZIP Code 27560	Telephone Number 919-456-7800
FAX Number (if available) 919-456-7850	E-Mail Address (if available) gail.mcintyre@furiex.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRASStaff@fda.hhs.gov

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

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7620 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

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

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

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

2. Drug Substance (Active Ingredient)

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

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

3. Drug Product (Composition/Formulation)

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

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

4. Method of Use

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

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Identify the precise words of the approval labeling that describe with specificity the patented method of use.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

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

**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

206940

NAME OF APPLICANT/NDA HOLDER

Furiex Pharmaceuticals, Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)

XENRYMA

ACTIVE INGREDIENT(S)

eluxadoline

STRENGTH(S)

75 mg
100 mg

DOSAGE FORM

75 and 100-mg tablets

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

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

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

FDA will not list patent information if you submit 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

8,609,709

b. Issue Date of Patent

December 17, 2013

c. Expiration Date of Patent

March 14, 2025

d. Name of Patent Owner

Janssen Pharmaceutica, N.V.

Address (of Patent Owner)

Turnhoutseweg 30

City/State

2340 Beerse

ZIP Code

Belgium

FAX Number (if available)

32 2 749 2558

Telephone Number

32 14 60 21 11

E-Mail Address (if available)

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

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

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

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

Yes

No

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

Yes

No

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

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) (as listed in the patent) Does (Do) the patent claim(s) 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 proposed 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



20 May 2014

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.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Gail McIntyre	
Address 3900 Paramount Parkway, Suite 150	City/State Morrisville, NC
ZIP Code 27560	Telephone Number 919-456-7800
FAX Number (if available) 919-456-7850	E-Mail Address (if available) gail.mcintyre@furiex.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRASStaff@fda.hhs.gov

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

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

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

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7620 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

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

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

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

2. Drug Substance (Active Ingredient)

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

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

3. Drug Product (Composition/Formulation)

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

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

4. Method of Use

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

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Identify the precise words of the approval labeling that describe with specificity the patented method of use.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

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

**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

206940

NAME OF APPLICANT/NDA HOLDER

Furiex Pharmaceuticals, Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)

XENRYMA

ACTIVE INGREDIENT(S)

eluxadoline

STRENGTH(S)

75 mg
100 mg

DOSAGE FORM

75 and 100-mg tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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

FDA will not list patent information if you submit 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

8,691,860

b. Issue Date of Patent

April 8, 2014

c. Expiration Date of Patent

July 7, 2028

d. Name of Patent Owner

Furiex Pharmaceuticals, Inc.

Address (of Patent Owner)

3900 Paramount Parkway, Suite 150

City/State

Morrisville, NC

ZIP Code

27560

FAX Number (if available)

919-456-7850

Telephone Number

919-456-7800

E-Mail Address (if available)

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

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

City/State

ZIP Code

Telephone Number

FAX Number (if available)

E-Mail Address (if available)

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

Yes

No

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

Yes

No

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

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
9	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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 proposed labeling.) XENRYMA (eluxadoline) is indicated for the treatment of diarrhea and abdominal pain in men and women with diarrhea predominant irritable bowel syndrome. The patent claims cover the use of eluxadoline to treat irritable bowel syndrome, or to treat pain.
---	--

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

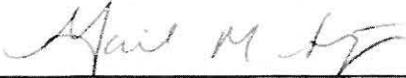
6. Declaration Certification

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



20 May 2014

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.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Gail McIntyre	
Address 3900 Paramount Parkway, Suite 150	City/State Morrisville, NC
ZIP Code 27560	Telephone Number 919-456-7800
FAX Number (if available) 919-456-7850	E-Mail Address (if available) gail.mcintyre@furiex.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

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

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- * To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
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- * Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- * Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- * Only information from form 3542 will be used for Orange Book publication purposes.
- * Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7620 Standish Place, Rockville, MD 20855.
- * The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- * Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

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

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

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

2. Drug Substance (Active Ingredient)

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

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

3. Drug Product (Composition/Formulation)

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

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

4. Method of Use

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

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Identify the precise words of the approval labeling that describe with specificity the patented method of use.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

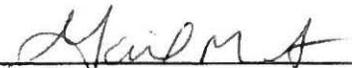
Complete all items in this section.

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

1.3.5.2 Patent Certification

1.3.5.2 Patent Certification

Furiex Pharmaceuticals, Inc. hereby certifies that the provisions of 21 U.S.C 355(b)(2) or (j)(2)(A) do not apply to this application.



Gail McIntyre

Senior Vice President, Research

Furiex Pharmaceuticals, Inc.

20 May 2014

Date

EXCLUSIVITY SUMMARY

NDA # 206940

SUPPL # N/A

HFD # 180

Trade Name Viberzi

Generic Name Eluxadoline

Applicant Name Furiex Pharmaceuticals, Inc.

Approval Date, If Known May 27, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES NO

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

5 years

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

YES NO

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

N/A

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA# N/A

NDA# N/A

NDA# N/A

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# N/A

NDA# N/A

NDA# N/A

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

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

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

interest provided substantial support for the study?

Investigation #1
!
! YES NO
! Explain: ! Explain:

Investigation #2
!
! YES NO
! Explain: ! Explain:

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

YES NO

If yes, explain:

Name of person completing form: Laurie Muldowney, M.D.
Title: Medical Officer, Division of Gastroenterology and Inborn Errors Products
Date: May 14, 2015

Name of Office/Division Director signing form: Office of Drug Evaluation III/Donna Griebel, M.D.
Title: Director, Division of Gastroenterology and Inborn Errors Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

JENNIFER S SARCHET
05/22/2015

DONNA J GRIEBEL
05/24/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 206940 BLA # N/A	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Eluxadoline Established/Proper Name: Viberzi Dosage Form: 75 mg and 100 mg Tablets		Applicant: Furiex Pharmaceuticals, Inc. Agent for Applicant (if applicable): N/A
RPM: Jennifer Sarchet		Division: DG1EP
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin-left: 20px;"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: N/A </p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>May 27, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received N/A.
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): mu-opioid receptor agonist
 (confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters

❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) Approval: June 27, 2015
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Labeling

❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
--	--

- Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)* Included 5/27/2015
- Original applicant-proposed labeling Included (June 27, 2014)

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
--	---

- Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)* Included (as of May 14, 2015)
- Original applicant-proposed labeling Included June 27, 2014

❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
--	--

- Most-recent draft labeling Included June 27, 2015

Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	4/28/2015, 4/27/2015, 2/2/2015, 9/5/2014
---	--

❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None 9/8/2014 DMEPA: <input type="checkbox"/> None 1/6/2015, 2/2/15, 9/5/2014 DMPP/PLT (DRISK): <input type="checkbox"/> None 4/27/2015 OPDP: <input type="checkbox"/> None 4/28/2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None 4/21/2015 (consult review – see Controlled Substance Staff (CSS) Review Section) Other: <input checked="" type="checkbox"/> None
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Administrative / Regulatory Documents

❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	9/10/2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)

❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included 5/24/2015
---	--

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>3/18/2015</u> If PeRC review not necessary, explain: <u>N/A</u> 	3/18/2015, 3/4/2015, 2/26/2015, 2/17/2015, 1/29/2015, 4/1/2014
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	5/15/2015, 5/14/2015, 5/14/2015, 5/14/2015, 5/8/2015, 5/5/2015, 4/30/2015, 4/30/2015, 4/29/2015, 3/4/2015, 2/24/2015, 2/17/2015, 2/17/2015, 2/12/2015, 2/3/2015, 2/2/2015, 2/2/2015, 1/29/2015, 1/16/2015, 1/16/2015, 12/31/2014, 12/24/2014, 12/8/2014, 12/4/2014, 12/1/2014, 12/1/2014, 11/25/2014, 11/21/2014, 11/21/2014, 11/12/2014, 10/21/2014, 9/5/2014, 9/23/2014, 9/11/2014, 8/28/2014, 8/27/2014, 8/19/2014, 8/11/2014, 8/8/2014, 7/11/2014
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	3/4/2015, 4/14/2015, 10/9/2014
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 4/22/2014
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 9/27/2011
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 12/10/2014
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 3/11/2015
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	2/25/2015 (Guidance: CSS)
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	N/A
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 5/27/2015
<ul style="list-style-type: none"> Division Director Summary Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 5/27/2015
<ul style="list-style-type: none"> Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 4/22/2015
<ul style="list-style-type: none"> PMR/PMC Development Templates (<i>indicate total number</i>) 	<input type="checkbox"/> None 9 total (4 PMRs and 5 PMCs)
Clinical	
<ul style="list-style-type: none"> ❖ Clinical Reviews 	
<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	5/26/2015, 2/25/2015, 8/16/2014

• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	5/26/2015, Clinical Review 2/25/2015 page 25 N/A
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> N/A 4/21/2015
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	N/A N/A <input type="checkbox"/> None 4/6/2015
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 2/11/2015 OSI Letter: 5/14/2015, 5/14/2015, 2/2/2015, 12/8/2014, 12/5/2014, 11/12/2014, 10/21/2014
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3/9/2015, 2/27/2015, 8/15/2014
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/27/2015, 3/30/2015, 8/15/2014
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)		<input type="checkbox"/> No separate review
• Supervisory Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)		<input type="checkbox"/> None 5/18/2015, 2/23/2015, 1/23/2015, 8/12/2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)		<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)		<input type="checkbox"/> No carc 9/24/2014
❖ ECAC/CAC report/memo of meeting		<input type="checkbox"/> None 3/16/2011 Included in P/T review, pages 187 - 226
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)		<input checked="" type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (indicate date for each review)		<input type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)		<input type="checkbox"/> None 3/4/2015, 2/10/2015, 8/19/2014
❖ Microbiology Reviews		<input type="checkbox"/> 8/1/2014
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)		Product Quality Review (CMC), page 214
<input type="checkbox"/> Review & FONSI (indicate date of review)		N/A
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)		N/A
❖ Facilities Review/Inspection		
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites ⁵)		Date completed: 1/15/2015 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)		Date completed: N/A <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

❖ NDAs: Methods Validation (*check box only, do not include documents*)

- Completed 1/22/2015
- Requested
- Not yet requested
- Not needed (per review)

Day of Approval Activities

<ul style="list-style-type: none"> ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
<ul style="list-style-type: none"> ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email 	<input checked="" type="checkbox"/> Done 5/27/2015
<ul style="list-style-type: none"> ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter 	<input checked="" type="checkbox"/> Done 5/27/2015
<ul style="list-style-type: none"> ❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name 	<input checked="" type="checkbox"/> Done 5/27/2015
<ul style="list-style-type: none"> ❖ Ensure Pediatric Record is accurate 	<input checked="" type="checkbox"/> Done 5/27/2015
<ul style="list-style-type: none"> ❖ Send approval email within one business day to CDER-APPROVALS 	<input checked="" type="checkbox"/> Done 5/27/2015

From: [Sarchet, Jennifer](#)
 To: ["Michelle Usher"](#)
 Subject: RE: NDA 206940; Viberzi (eluxadoline): Applicant Labeling Questions: Responses
 Date: Friday, May 15, 2015 3:08:17 PM

Dear Michelle,

Please refer to NDA 206940; Viberzi (eluxadoline). We have the following responses regarding your questions about the PI dated May 13, 2015.

Applicant Questions: We note that the agency has requested that we delete [redacted] (b) (4). The Sponsor requests clarity on the specific basis for deletion of certain text for which this directive may not apply. Specifically:

1. The description of the monthly interval data was based on prospective analyses conducted at the individual study level. These data provide important clinical information on the time course and durability of response.

FDA Response: We have considered the justifications that you have provided and agreed with inclusion of the following descriptive sentence of the monthly interval data: "Additionally, the proportion of patients who were composite responders to VIBERZI at each 4-week interval [redacted] (b) (4) was numerically higher in both [redacted] (b) (4) [redacted] (b) (4) "

Our position remains unchanged for the remainder of the paragraph [redacted] (b) (4). Specifically, we do not agree with [redacted] (b) (4)

2. [redacted] (b) (4)

FDA Response: We have considered the justifications that you have provided, and our opinion remains that [redacted] (b) (4) should not be described in the labeling. Moreover, we do not believe [redacted] (b) (4)

3. We did not get a response from FDA regarding our rationale for leaving some of the text in as proposed (Seq 0031).

FDA Response: Please see above responses.

4. Also FDA denotes in the comment field in [redacted] (b) (4) of the label that the [redacted] (b) (4) are "invalid"?

FDA Response: This statement is not considered valid for inclusion in the label [redacted] (b) (4). Please refer to meeting minutes dated December 6, 2013 for IND 079214 for JNJ-27018966 (eluxadoline).

5. Lastly, FDA has made changes to text that they had proposed in the 29 April label version.

Please see below for examples:

Labeling Section	FDA Comment/Revision (30 April 2015)	FDA Comment/Revision (13 May 2015)	FDA Response
Highlights and Description (Section 11)	[redacted] (b) (4)		
Warnings and Precautions (Section 5) and Adverse Reactions (Section 6)			

(b) (4)

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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From: Michelle Usher [mailto:Michelle.Usher@furiex.com]
Sent: Friday, May 15, 2015 1:12 PM
To: Sarchet, Jennifer
Subject: RE: NDA 206940; Viberzi (eluxadoline): PI and MG as of May 13, 2015

Hi Jennifer,
Since we did not hear back from you as requested this morning, we are proceeding with a written response to the labeling comments. Please let me know if I should hold off sending it since it appears FDA is looking at the earlier labeling comments as you noted below.
Thanks,
Michelle

From: Sarchet, Jennifer [mailto:Jennifer.Sarchet@fda.hhs.gov]
Sent: Thursday, May 14, 2015 2:05 PM
To: Michelle Usher
Subject: RE: NDA 206940; Viberzi (eluxadoline): PI and MG as of May 13, 2015

Michelle,

- The team is actively looking at the label and your questions. Could you clarify what texts you are referring to when you say, "Lastly, FDA has made changes to text that they had proposed in the 29 April label version."

Thank you,
Jennifer

From: Michelle Usher [mailto:Michelle.Usher@furiex.com]
Sent: Thursday, May 14, 2015 1:08 PM
To: Sarchet, Jennifer
Subject: RE: NDA 206940; Viberzi (eluxadoline): PI and MG as of May 13, 2015

Hi Jennifer,
Any luck in getting us a teleconference? Without a clear understanding of FDA's rationale, our response will not be that different from what we have provided before; therefore, I fear we will not be any closer in reaching a final, agreed-upon label. Since a call today is unlikely, we will need confirmation by tomorrow morning regarding the capability for a teleconference in order for us to prepare a written response.
Thanks,
Michelle

From: Michelle Usher
Sent: Wednesday, May 13, 2015 1:52 PM

To: 'Sarchet, Jennifer'
Subject: RE: NDA 206940; Viberzi (eluxadoline); PI and MG as of May 13, 2015

Hi Jennifer,

Yes, the questions will be the same. We did not get a response from FDA regarding our rationale for leaving some of the text in as proposed (Seq 0031). Also FDA denotes in the comment field in (b) (4) of the label that the (b) (4) are "invalid"? Lastly, FDA has made changes to text that they had proposed in the 29 April label version.

Please do what you can to get a teleconference as soon as possible.

Thanks,
Michelle

From: Sarchet, Jennifer [mailto:Jennifer.Sarchet@fda.hhs.gov]
Sent: Wednesday, May 13, 2015 1:30 PM
To: Michelle Usher
Subject: RE: NDA 206940; Viberzi (eluxadoline); PI and MG as of May 13, 2015

Michelle,

Could you provide a list of items to discuss? Are they any different than the previous ones you sent below?

We note that the agency has requested that we delete (b) (4). The Sponsor requests clarity on the specific basis for deletion of certain text for which this directive may not apply. Specifically:

- The description of the monthly interval data was based on prospective analyses conducted at the individual study level. These data provide important clinical information on the timecourse and durability of response.

- (b) (4)

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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240-402-4275 (office)

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From: Michelle Usher [mailto:Michelle.Usher@furiex.com]
Sent: Wednesday, May 13, 2015 1:12 PM
To: Sarchet, Jennifer
Subject: RE: NDA 206940; Viberzi (eluxadoline); PI and MG as of May 13, 2015

Jennifer,

We really require a teleconference with FDA to discuss these comments. I am afraid without such we will not be able to reach agreement on the labeling language in the timeframe needed. Please let me know a time available to discuss.

Thanks,
Michelle

From: Sarchet, Jennifer [mailto:Jennifer.Sarchet@fda.hhs.gov]
Sent: Wednesday, May 13, 2015 1:03 PM
To: Michelle Usher
Subject: RE: NDA 206940; Viberzi (eluxadoline); PI and MG as of May 13, 2015
Importance: High

Michelle,

Please refer to NDA 206940; Viberzi (eluxadoline). Attached are the current PI and MG (in word and PDF track changes versions). We request your response as soon as possible, preferable by COB on May 14, 2015, if possible.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

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From: Michelle Usher [<mailto:Michelle.Usher@furiex.com>]
Sent: Thursday, May 07, 2015 4:55 PM
To: Sarchet, Jennifer
Subject: RE: NDA 206940; Viberzi (eluxadoline); PI and MG

Hi Jennifer,

As requested, here is a copy of Seq 0030 which includes the cover letter and the PI and MG in Word (both clean and tracked changes) The PDF and Word versions are being formally submitted to the NDA later today

Please let me know if you have any questions

Thanks,

Michelle

From: Sarchet, Jennifer [<mailto:Jennifer.Sarchet@fda.hhs.gov>]
Sent: Thursday, April 30, 2015 11:29 AM
To: Michelle Usher
Subject: NDA 206940; Viberzi (eluxadoline); PI and MG
Importance: High

Dear Michelle,

Please refer to NDA 206940; Viberzi (eluxadoline). Attached are the current Prescribing Information (PI) and the current Medication Guide (MG). Word and PDF versions in track changes have been provided for both. As we quickly approach the PUDFA date, we great appreciate a speedy turnaround of not later than COB on May 7th.

I plan to send the PMRs/PMCs later today.

Please let me know if you have any questions.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
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/s/

JENNIFER S SARCHET
05/15/2015

From: [Sarchet, Jennifer](#)
To: "Michelle Usher"
Subject: RE: NDA 206940; Viberzi (eluxadoline); PI and MG as of May 13, 2015
Date: Wednesday, May 13, 2015 1:02:43 PM
Attachments: [Current NDA 206940 draft_package_insert_tracked 5-13-2015.doc](#)
[Current NDA 206940 draft_package_insert_tracked 5-13-2015.pdf](#)
[Current NDA 206940 draft_medication_guide_tracked 5-13-2015.docx](#)
[Current NDA 206940 draft_medication_guide_tracked 5-13-2015.pdf](#)
Importance: High

Michelle,

Please refer to NDA 206940; Viberzi (eluxadoline). Attached are the current PI and MG (in word and PDF track changes versions). We request your response as soon as possible, preferable by COB on May 14, 2015, if possible.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
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From: Michelle Usher [mailto:Michelle.Usher@furiex.com]
Sent: Thursday, May 07, 2015 4:55 PM
To: Sarchet, Jennifer
Subject: RE: NDA 206940; Viberzi (eluxadoline); PI and MG

Hi Jennifer,

As requested, here is a copy of Seq 0030 which includes the cover letter and the PI and MG in Word (both clean and tracked changes). The PDF and Word versions are being formally submitted to the NDA later today.

Please let me know if you have any questions.

Thanks,
Michelle

From: Sarchet, Jennifer [<mailto:Jennifer.Sarchet@fda.hhs.gov>]
Sent: Thursday, April 30, 2015 11:29 AM
To: Michelle Usher
Subject: NDA 206940; Viberzi (eluxadoline); PI and MG
Importance: High

Dear Michelle,

Please refer to NDA 206940; Viberzi (eluxadoline). Attached are the current Prescribing Information (PI) and the current Medication Guide (MG). Word and PDF versions in track changes have been provided for both. As we quickly approach the PUDFA date, we great appreciate a speedy turnaround of not later than COB on May 7th.

I plan to send the PMRs/PMCs later today.

Please let me know if you have any questions.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
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240-402-4275 (office)

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/s/

JENNIFER S SARCHET
05/14/2015

From: [Sarchet, Jennifer](#)
To: "[Michelle Usher](#)"
Subject: NDA 206940; Viberzi (eluxadoline); Biopharm PMC
Date: Friday, May 08, 2015 12:24:30 PM
Attachments: [Biopharm NDA 206940-PMC 1.doc](#)
[Biopharm NDA 206940-PMC 1.pdf](#)
Importance: High

Dear Michelle,

Please refer to NDA 206940; Viberzi (eluxadoline). We have one final Biopharm PMC to add. Please see attached and notify me of your concurrence as soon as possible.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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From: [Sarchet, Jennifer](#)
To: "Michelle Usher"
Subject: RE: NDA 206940; Viberzi (eluxadoline); PI and MG
Date: Tuesday, May 05, 2015 2:46:42 PM

Hello Michelle,

Please refer see the Division's response to your questions below for NDA 206940; Viberzi (eluxadoline) regarding the PI.

Applicant Question 1: We note that the agency has requested that we delete (b) (4)

The Sponsor requests clarity on the specific basis for deletion of certain text for which this directive may not apply. Specifically:

The description of the monthly interval data was based on prospective analyses conducted at the individual study level. These data provide important clinical information on the time course and durability of response.

Applicant Question 2: (b) (4)

FDA Response: (b) (4)

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps

Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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From: Michelle Usher [mailto:Michelle.Usher@furiex.com]
Sent: Friday, May 01, 2015 4:37 PM
To: Sarchet, Jennifer
Subject: RE: NDA 206940; Viberzi (eluxadoline); PI and MG

Hi Jennifer,

Here is our question.....

We note that the agency has requested that we delete [REDACTED] (b) (4)
[REDACTED] The Sponsor requests clarity on the specific basis for deletion of certain text for which this directive may not apply. Specifically:

- The description of the monthly interval data was based on prospective analyses conducted at the individual study level. These data provide important clinical information on the timecourse and durability of response.

- [REDACTED] (b) (4)

Thanks,
Michelle

From: Michelle Usher
Sent: Friday, May 01, 2015 3:49 PM
To: 'Sarchet, Jennifer'
Subject: RE: NDA 206940; Viberzi (eluxadoline); PI and MG

I should have the general questions for you shortly but the topic is around FDA's deletion [REDACTED] (b) (4)

From: Sarchet, Jennifer [<mailto:Jennifer.Sarchet@fda.hhs.gov>]
Sent: Friday, May 01, 2015 3:05 PM
To: Michelle Usher
Subject: RE: NDA 206940; Viberzi (eluxadoline); PI and MG

Michelle,

Did you already send the questions?

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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From: Michelle Usher [<mailto:Michelle.Usher@furiex.com>]
Sent: Friday, May 01, 2015 2:57 PM
To: Sarchet, Jennifer
Subject: RE: NDA 206940; Viberzi (eluxadoline); PI and MG

Jennifer,

Thanks for getting responses back to me on my earlier questions. Have you been able to secure a teleconference for Tuesday yet? We need to discuss FDA comments made in the (b) (4) of the label specifically. We also have 1 or 2 clarifications based on FDA's edits in the label.

Thanks,
Michelle

From: Sarchet, Jennifer [<mailto:Jennifer.Sarchet@fda.hhs.gov>]
Sent: Thursday, April 30, 2015 1:11 PM

To: Michelle Usher
Subject: RE: NDA 206940; Viberzi (eluxadoline); PI and MG

Please send your questions and I will forward to the team along with your request for a meeting.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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From: Michelle Usher [<mailto:Michelle.Usher@furiex.com>]
Sent: Thursday, April 30, 2015 1:10 PM
To: Sarchet, Jennifer
Subject: RE: NDA 206940; Viberzi (eluxadoline); PI and MG
Importance: High

Thanks Jennifer.

We would like to discuss some of these comments with FDA prior to 07 May 2015 response. Would a teleconference on Tuesday work? I expect that our questions would center around the (b) (4) of the label and will be sending you questions/rationale ahead of the call. Please let me know what time works best for your colleagues.

Thanks,
Michelle

From: Sarchet, Jennifer [<mailto:Jennifer.Sarchet@fda.hhs.gov>]
Sent: Thursday, April 30, 2015 11:29 AM
To: Michelle Usher
Subject: NDA 206940; Viberzi (eluxadoline); PI and MG
Importance: High

Dear Michelle,

Please refer to NDA 206940; Viberzi (eluxadoline). Attached are the current Prescribing Information (PI) and the current Medication Guide (MG). Word and PDF versions in track changes have been provided for both. As we quickly approach the PUDFA date, we great appreciate a speedy turnaround of not later than COB on May 7th.

I plan to send the PMRs/PMCs later today.

Please let me know if you have any questions.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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/s/

JENNIFER S SARCHET
05/05/2015

From: [Sarchet, Jennifer](#)
To: ["Michelle Usher"](#)
Subject: NDA 206940; Viberzi (eluxadoline); PMRs/PMCs
Date: Thursday, April 30, 2015 11:56:42 AM
Attachments: [NDA 206940 eluxadoline PMRs and PMCs to the Applicant 4-30-2015.docx](#)
[NDA 206940 eluxadoline PMRs and PMCs to the Applicant 4-30-2015.pdf](#)

Dear Michelle,

Please refer to NDA 206940; Viberzi (eluxadoline). Attached are the current PMRs/PMCs. Word and PDF versions are provided. We appreciate a response not later than COB on May 4, 2015 if at all possible.

Please let me know if you have any questions.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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/s/

JENNIFER S SARCHET
04/30/2015

From: [Sarchet, Jennifer](#)
To: "Michelle Usher"
Subject: NDA 206940; Viberzi (eluxadoline); PI and MG
Date: Thursday, April 30, 2015 11:29:18 AM
Attachments: [Final CURRENT LABEL Eluxadoline PI to Applicant4-30-15.doc](#)
[Final CURRENT LABEL Eluxadoline PI to Applicant4-30-15.pdf](#)
[Final Currrent MG eluxadoline NDA 206940 to Applicant Apr 30 2015.docx](#)
[Final Currrent MG eluxadoline NDA 206940 to Applicant Apr 30 2015.pdf](#)
Importance: High

Dear Michelle,

Please refer to NDA 206940; Viberzi (eluxadoline). Attached are the current Prescribing Information (PI) and the current Medication Guide (MG). Word and PDF versions in track changes have been provided for both. As we quickly approach the PUDFA date, we great appreciate a speedy turnaround of not later than COB on May 7th.

I plan to send the PMRs/PMCs later today.

Please let me know if you have any questions.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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/s/

JENNIFER S SARCHET
04/30/2015

From: [Sarchet, Jennifer](#)
To: "Michelle Usher"
Subject: NDA 206940; Eluxadoline; Request for Information Intended to Populate the FDA Drug Trials Snapshot Website
Date: Wednesday, April 29, 2015 10:55:39 AM
Attachments: [Copy of Tables--eluxadoline.xls](#)

Dear Michelle,

We are requesting your assistance in populating the attached tables for your New Molecular Entity, eluxadoline, currently under review in the Division. If the application is approved, this information will be posted publically at the FDA drug snapshot website:

<http://www.fda.gov/drugtrialsnapshot>.

The purpose of the drug trials snapshot website is to provide consumers with information about who participated in clinical trials that supported the FDA approval of new drugs. The website will include information on study design, results of efficacy and safety studies, and whether there were any differences in efficacy and side effects within sex, race, and age subgroups. The website is not intended to replace or replicate the package insert (PI), which is intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language
- Information that focuses on subgroup data and analyses
- Links to the PI for the product and to the FDA reviews at Drugs@FDA

Information will be published to the Drug Trials Snapshot website approximately 30 days after drug approval. Therefore, we are requesting that you complete the attached tables as well as provide descriptions of the analyses used to generate the data. We are requesting you submit this information no later than 13 May 2015.

Thank you in advance for your cooperation.

Please let me know if you have any questions.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA

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Table 6.1.1 Listing of Clinical Trials for the Efficacy Analysis

Study ID	No. of patients enrolled in Treatment	No. of patients enrolled in Control

Table 6.1.2-b. Baseline Demographics, Multiple Pivotal Efficacy Trials (categories can be modified to match pro

Demographic Parameters	Trial #1		Trial #2		Total (N=200)
	Treatment (N=50) n (%)*	Control (N=50) n (%)*	Treatment (N=50) n (%)*	Control (N=50) n (%)*	
Sex					
Male					
Female					
Age					
Mean years (SD)					
Median (years)					
Min, Max (years)					
Age Group					
<17 years					
>=17 - <65 years					
>=65 years					
>=75 years					
Race					
White					
Black or African American					
Asian					
American Indian or Alaska Native					
Native Hawaiian or Other Pacific Islander					
Other					
Ethnicity					
Hispanic or Latino					
Not Hispanic or Latino					
Region					
United States					
Rest of the World					
Canada					
South America					
Europe					
Asia					
Africa					

Source:

* Percentages are calculated based on the total number of subjects in the respective arm. For example, percenta

ogram's categories)

Appears this way on original

age of males in Treatment Group of Trial 1 = 30/50

Table 6.1.7 Subgroup Analysis of Primary Endpoint, Pivotal Efficacy Trials (need one table for each piv

Subgroup	Treatment		Control	
	x (%)*	Total, n	x (%)*	Total, n
Overall Response/All patients				
Sex				
Male				
Female				
Age Group				
<17 years				
>=17 - <65 years				
>=65 years				
>=75 years				
Race				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Region				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source:

*Percentages are calculated based on the number of subjects in the subgroup per arm. For example, per

**Designated per review, other options are Risk Difference, Relative Risk, etc

Table 7.2.1-b. Baseline Demographics, Multiple Trials, Safety Population (complete is safety population for

Demographic Parameters	Trial #1		Trial #2		Total (N=200)
	Treatment (N=50) n (%)*	Control (N=50) n (%)*	Treatment (N=50) n (%)*	Control (N=50) n (%)*	
Sex					
Male					
Female					
Age					
Mean years (SD)					
Median (years)					
Min, Max (years)					
Age Group					
<17 years					
>=17 - <65 years					
>=65 years					
>=75 years					
Race					
White					
Black or African American					
Asian					
American Indian or Alaska Native					
Native Hawaiian or Other Pacific Islander					
Other					
Ethnicity					
Hispanic or Latino					
Not Hispanic or Latino					
Region					
United States					
Rest of the World					
Canada					
South America					
Europe					
Asia					
Africa					

Source:

* Percentages are calculated based on the total number of subjects in the respective arm. For example, perc

pivotal trials is different than efficacy population)

Appears this way on original

Percentage of males in Treatment Group of Trial 1 = 30/50

Table 7.5.3-a. Subgroup Analysis of AEs, Safety Population (complete similar table for SOC Gastrointestin

Subgroup	Treatment		Control		Relative Risk***	95% CI	
	x (%)**	Total, n	x (%)**	Total, n		LL	UL
Any TEAEs*							
Sex							
Male							
Female							
Age Group							
<17 years							
>=17 - <65 years							
>=65 years							
>=75 years							
Race							
White							
Black or African American							
Asian							
American Indian or Alaska Native							
Native Hawaiian or Other Pacific Islander							
Other							
Ethnicity							
Hispanic or Latino							
Not Hispanic or Latino							
Region (
United States							
Rest of the World							
Canada							
South America							
Europe							
Asia							
Africa							

Source:

*Designate per review, other options are SAEs or AEs of special interest (for instance, an HLT, SOC, or user-

** Percentages are calculated based on the number of subjects in the subgroup per arm. For example, perc

***Designated per review, other options are Risk Difference, Hazard Ratios, etc

al Disorders, do not include all Preferred Terms)

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designated group of PTs)
centage of males with TEAEs in treatment group = 25/30

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/s/

JENNIFER S SARCHET
04/29/2015



NDA 206940

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Furiex Pharmaceuticals, Inc.
3900 Paramount Parkway, Suite 150
Morrisville, NC 27560

ATTENTION: Michelle P. Usher, RAC
Executive Director, Regulatory Affairs

Dear Ms. Usher:

Please refer to your New Drug Application (NDA) dated June 26, 2014, received June 27, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eluxadoline Tablets, 75 mg and 100 mg.

We also refer to your correspondence, dated and received February 12, 2015, requesting review of your proposed proprietary name, Viberzi.

We have completed our review of the proposed proprietary name, Viberzi and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your February 12, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5295. For any other information regarding this application, contact Jennifer Sarchet, Regulatory Project Manager in the Office of New Drugs, at (240) 402-4275

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR on behalf of TODD D BRIDGES
04/28/2015

PeRC Meeting Minutes
March 18, 2015

PeRC Members Attending:

Lynne Yao
Robert "Skip" Nelson
Wiley Chambers
Rosemary Addy
George Greeley
Ruthanna Davi
Tom Smith
Karen Davis-Bruno
Daiva Shetty
Andrew Mulberg
Greg Reaman
Efe Eworuke
Hari Cheryl Sachs
Julia Pinto
Kristiana Brugger
Lily Mulugeta
Kevin Krudys
Barbara Buch
Rachel Witten
Dianne Murphy
Maura O'Leary

Agenda

(b) (4)

10:10 | NDA | 206940 | Eluxadoline Partial Waiver/Deferral/Plan | Treatment of irritable bowel syndrome with diarrhea | (b) (4)

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Eluxadoline Partial Waiver/Deferral/Plan

- Proposed Indications: Treatment of irritable bowel syndrome with diarrhea (IBS-D)
- The Division noted that there are currently no approved products to treat IBS-D in pediatric patients. Furthermore, the only approved product, Lotronex, includes a REMS and is only approved to treat women with IBS-D due to serious safety concerns. Additionally, the division noted that IBS-D is uncommon in patients less than 6 years of age and agrees with the sponsor's plan to waive studies in patients less than 6 years of age.
- PeRC Recommendations:
 - The PeRC agrees with the divisions recommendation to the plan for waiver of studies in patients less than 6 years of age
 - The PeRC also recommends that division continue discussion with the sponsor about the optimal study design for this condition in pediatric patients. The PeRC acknowledged the division's concern about the potential for high placebo response rates for this condition.

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/s/

GEORGE E GREELEY
04/14/2015



NDA 206940

MEETING MINUTES

Furiex Pharmaceuticals, Inc.
Attention: Michelle P. Usher, RAC
Executive Director, Regulatory Affairs
3900 Paramount Parkway Suite 150
Morrisville, North Carolina 27560

Dear Ms. Usher:

Please refer to your New Drug Application (NDA) dated June 27, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eluxadoline.

We also refer to the meeting between representatives of your firm and the FDA on February 25, 2015. The purpose of the meeting was to discuss questions and findings of the Agency's Controlled Substance Staff.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, Regulatory Project Manager at 240-402-4275.

Sincerely,

{See appended electronic signature page}

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance: Controlled Substance Staff (CSS)

Meeting Date and Time: February 25, 2015, 3:00 pm – 4:00 pm ET
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Application Number: 206940
Product Name: Eluxadoline
Indication: Treatment of irritable bowel syndrome with diarrhea in adults
Sponsor/Applicant Name: Furiex Pharmaceuticals, Inc.

Meeting Chair: Michael Klein, Ph. D., Director, Controlled Substance Staff Team Leader

Meeting Recorder: Jennifer Sarchet RN, BSN, MSHA, Regulatory Project Manager, Division of Gastroenterology and Inborn Errors Products (DGIEP)

FDA ATTENDEES

Julie Beitz, M.D., Director, Office of Drug Evaluation III
Amy G. Egan, M.D., Deputy Director (Acting), Office of Drug Evaluation III
Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Dragos Roman, M.D., Acting Deputy Director, DGIEP
Andrew E. Mulberg, M.D., Acting Associate Director, Rare Diseases Program, Division Deputy Director, DGIEP
Joyce Korvick, M.D., M.P.H., Deputy Director for Safety, DGIEP
Ruyi He, M.D., DGIEP
Laurie Muldowney, M.D., Medical Officer, DGIEP
Michael Klein, Ph. D., Director, Controlled Substance Staff Team Leader
Alan Trachtenberg, M.D., Medical Officer, Controlled Substance Staff Reviewer
Silvia N. Calderon, Ph.D., Team Leader Pharmacology, Controlled Substance Staff
Jennifer Sarchet RN, BSN, MSHA, Regulatory Project Manager, DGIEP

SPONSOR ATTENDEES

David Nicholson, Ph.D., Executive Vice President, Global Brands, Research and Development

June Bray, Ph.D., M.B.A., Senior Vice President, Global Regulatory Affairs
Gary Samoriski, Ph.D., Executive Director, Project Management and Planning
Steven Shiff, M.D., Executive Director, Clinical Development, Therapeutic Area Head, GI
Michelle Usher, R.A.C., Executive Director, Regulatory Affairs
Scott Dove, Ph.D., Executive Director, Clinical Operations
Tim Costello, Ph.D., Senior Director, Chemistry

(b) (4) Consultant, (b) (4)
(b) (4) ., Consultant, (b) (4)
(b) (4)
(b) (4)

1.0 BACKGROUND

On January 12, 2015, Furiex Pharmaceuticals, Inc. requested a meeting with the Agency's Controlled Substance Staff to review questions and findings related to CSS. The Agency granted this meeting as a type C meeting.

2. DISCUSSION

2.1. Controlled Substance Staff

Item 1: The main issue is that the schedule recommendation CSS is making (b) (4)

(b) (4)

- a. Required findings for Schedule II: High potential for abuse, Currently accepted medical use in the US, Abuse may lead to severe psychological or physical dependence.
- b. Schedule III: Abuse potential is less than drugs or other substances in Schedule II and abuse may lead to moderate or low physical dependence or high psychological dependence.
- c. Schedule IV: Abuse potential is low relative to substances in Schedule III and abuse may lead to limited physical dependence or psychological dependence relative to substances in Schedule III.
- d. Schedule V: Abuse potential is low relative to substances in Schedule IV and abuse may lead to limited physical dependence or psychological dependence relative to substances in Schedule IV.

Item 2: In studies, Eluxadoline has only been compared in studies to Schedule II opioids, primarily oxycodone. (b) (4)

- a. For example, filtered extractions using pH 2 buffer were able to recover approximately 65% of drug after an hour. Similarly, water extraction led to recovery of about 47% of the eluxadoline API after an hour. Thus, 5 tablets extracted in water would yield about (b) (4) mg of drug.

Item 3: The arguments raised by the company repeatedly return (b) (4)

However, data used to support this view are flawed.

Item 4: Our key concern is whether opioid abusers, given access to injectable eluxadoline, would persistently inject it. Based on the primate data, the answer to this key question seems to be yes, or at least it looks very likely.

Item 5: Monkeys discriminate injected eluxadoline as a Mu opioid and work for continued injections of it. In the absence of contradictory data of some sort, it must be assumed that human opioid abusers would probably self-inject it as well. The kind of human self-injection studies that might contradict this would not be safe enough to be ethically acceptable.

Item 6: The human intranasal insufflation study is not reassuring: using ground up product with inadequately characterized particle size did not lead to high enough systemic levels to find central effects if they would have been there to find. The nasal study might have been done with API to attain adequate blood levels to demonstrate or disprove central effects, but this was not done, despite CSS recommendation to do so. Additionally, Sponsor could have tested a larger dose if they had tested API as CSS recommended. Recreational drug users report, on average, snorting up to 500 mg powder comfortably and have been shown to be able to snort up to 900 mg of powder in previous studies. Study is limited by the limitation of maximum dose administered. Most of the substance administered intranasally was comprised of inert excipients.

Item 7: It looks like the dislike is a result of local effects of the ground up product, rather than any negative central effect of the API. “Euphoric mood” was reported in 21.9% and 18.8% of subjects after 100 mg and 200 mg eluxadoline, respectively.

This was lower than rates of euphoric mood after 15 mg and 30 mg oxycodone (43.8% and 65.6%, respectively). The only other AE reported that is related to abuse potential was somnolence, which was reported in 12.5% and 15.6% of subjects after 100 mg and 200 mg eluxadoline, respectively.

	Elux100	Elux200	Oxy15	Oxy30	PLAOXY	PlaJNJ
Euphoric mood:	7 (21.9%)	6 (18.8%)	14 (43.8%)	21(65.6%)	0 (0.0%)	0 (0.0%)

Source: CPS-1010

Item 8: The oral abuse study results also are not reassuring, and even suggest some signal of reward at the 1000 mg dose level.

	Elux100	Elux300	Elux1000	Oxy30	Oxy60	Placebo
Euphoric mood:	5 (14.3%)	7 (19.4%)	10 (27.8%)	28 (75.7%)	27 (73.0%)	2 (5.4%)

Source: CPS-1006

Item 9: The true test of abuse potential will come with the social experiment occurring over the first year of the drug's public availability: How many reports will be found of illicit drug users (and/or their suppliers) diverting, synthesizing, or otherwise obtaining and repeatedly injecting eluxadoline in some form? This is a natural social experiment which will occur whether the drug is scheduled or not. This will be easier to spot, but do correspondingly more harm, if the drug is not scheduled on introduction.

Item 10: Opioid agonists (including partial or mixed agonist opioids) of lesser but still significant central effect have been on occasion introduced without initial scheduling and almost all have ended up needing to be scheduled, based on this population experiment. The concern is not so much whether patients started on eluxadoline will become iatrogenically addicted. The concern is that this new molecule may well become another injectable vector in the opiate abusing population for infections with HBV, HCV, HIV, bacterial endocarditis, overdose deaths, and other medical complications of injection drug abuse in the vulnerable population.

Item 11: The primate injection data support the need to schedule Eluxadoline. CSS recommends that the drug-related harm to be caused by the drug be minimized from the beginning, rather than awaiting the next replication of the traditional social experiment that occurs with the introduction of new centrally active mu opioids.

Discussion: The applicant agreed that the available data suggests that Eluxadoline has abuse potential and should be scheduled. The applicant agreed to re-submit a revised proposal for scheduling and an Eight Factor Analysis proposing a Schedule IV. The updated Eight Factor Analysis will include data from the GLP toxicology study to address physical dependence. They will also provide additional supportive data from the intranasal study in which the applicant believes will support a Schedule IV level of control under the Controlled Substances Act (CSA). The recommendation on scheduling will be dependent upon review of this data.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Applicant agreed to re-submit a revised proposal for scheduling and an Eight Factor Analysis (to include data from the GLP toxicology study to address physical dependence).	Applicant	Not determined
Applicant agreed to provide additional supportive data from the intranasal study.	Applicant	Not determined

6.0 ATTACHMENTS AND HANDOUTS

Agenda for Face to Face Meeting for NDA 206940; eluxadoline

Date: February 25, 2015

Time: 3:00 pm – 4:00 pm ET

Location: 10903 New Hampshire Avenue

White Oak Building 22, Conference Room: 1421

Silver Spring, Maryland 20903

1. Introductions (5 mins)
2. Brief explanation of Scheduling Process (5 mins)
3. CSS Data Analysis (10 mins)
4. CSS Scheduling Recommendation (5 mins)
5. Applicant Comments/Questions (10 mins)
6. Next Steps/Available Options (10 mins)
7. Discussion/Closing (15 mins)

Eluxadoline (NDA 206940) Abuse Potential & Scheduling

CSS Talking Points

- 1) The main issue is that the schedule recommendation CSS is making [REDACTED] (b) (4)
[REDACTED]
 - a. Required findings for Schedule II: High potential for abuse, Currently accepted medical use in the US, Abuse may lead to severe psychological or physical dependence.
 - b. Schedule III: Abuse potential is less than drugs or other substances in Schedule II and abuse may lead to moderate or low physical dependence or high psychological dependence.
 - c. Schedule IV: Abuse potential is low relative to substances in Schedule III and abuse may lead to limited physical dependence or psychological dependence relative to substances in Schedule III.
 - d. Schedule V: Abuse potential is low relative to substances in Schedule IV and abuse may lead to limited physical dependence or psychological dependence relative to substances in Schedule IV.
- 2) In studies, Eluxadoline has only been compared in studies to Schedule II opioids, primarily oxycodone. [REDACTED] (b) (4)
[REDACTED]
 - a. For example, filtered extractions using pH 2 buffer were able to recover approximately 65% of drug after an hour. Similarly, water extraction led to recovery of about 47% of the eluxadoline API after an hour. Thus, 5 tablets extracted in water would yield about [REDACTED] (b) (4) mg of drug.
- 3) The arguments raised by the company repeatedly return to [REDACTED] (b) (4)
[REDACTED]
[REDACTED]. However, data used to support this view are flawed.
- 4) Our key concern is [REDACTED] (b) (4)
[REDACTED].

- 5) Monkeys discriminate injected eluxadoline as a Mu opioid and work for continued injections of it. (b) (4)

The kind of human self-injection studies that might contradict this would not be safe enough to be ethically acceptable.

- 6) The human intranasal insufflation study is not reassuring: using ground up product with inadequately characterized particle size did not lead to high enough systemic levels to find central effects if they would have been there to find. The nasal study might have been done with API to attain adequate blood levels to demonstrate or disprove central effects, but this was not done, despite CSS recommendation to do so. Additionally, Sponsor could have tested a larger dose if they had tested API as CSS recommended. Recreational drug users report, on average, snorting up to 500 mg powder comfortably and have been shown to be able to snort up to 900 mg of powder in previous studies. Study is limited by the limitation of maximum dose administered. Most of the substance administered intranasally was comprised of inert excipients.
- 7) It looks like the dislike is a result of local effects of the ground up product, rather than any negative central effect of the API. “Euphoric mood” was reported in 21.9% and 18.8% of subjects after 100 mg and 200 mg eluxadoline, respectively.

This was lower than rates of euphoric mood after 15 mg and 30 mg oxycodone (43.8% and 65.6%, respectively). The only other AE reported that is related to abuse potential was somnolence, which was reported in 12.5% and 15.6% of subjects after 100 mg and 200 mg eluxadoline, respectively.

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Euphoric mood:	7 (21.9%)	6 (18.8%)	14 (43.8%)	21(65.6%)	0 (0.0%)	0 (0.0%)

Source: CPS-1010

- 8) The oral abuse study results also are not reassuring, and even suggest some signal of reward at the 1000 mg dose level.

	Elux100	Elux300	Elux1000	Oxy30	Oxy60	Placebo
Euphoric mood:	5 (14.3%)	7 (19.4%)	10 (27.8%)	28 (75.7%)	27 (73.0%)	2 (5.4%)

Source: CPS-1006

- 9) The true test of abuse potential will come with the social experiment occurring over the first year of the drug’s public availability: How many reports will be found of illicit drug users (and/or their suppliers) diverting, synthesizing, or otherwise obtaining and repeatedly injecting eluxadoline in some form? This is a natural social experiment which will occur whether the drug is scheduled or not. This will be easier to spot, but do correspondingly more harm, if the drug is not scheduled on introduction.

- 10) Opioid agonists (including partial or mixed agonist opioids) of lesser but still significant central effect have been on occasion introduced without initial scheduling and almost all have ended up needing to be scheduled, based on this population experiment. The concern is not so much whether patients started on eluxadoline will become iatrogenically addicted. The concern is that this new molecule may well become another injectable vector in the opiate abusing population for infections with HBV, HCV, HIV, bacterial endocarditis, overdose deaths, and other medical complications of injection drug abuse in the vulnerable population.
- 11) The primate injection data support the need to schedule Eluxadoline. CSS recommends that the drug-related harm to be caused by the drug be minimized from the beginning, rather than awaiting the next replication of the traditional social experiment that occurs with the introduction of new centrally active mu opioids.

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/s/

JENNIFER S SARCHET
03/06/2015

Note: The PeRC review of this product will likely occur *after* the Review Division checks this completed document into DARRTS. The PeRC's recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. PeRC meeting minutes are linked in DARRTS to the INDs and applications discussed during each meeting.

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

Complete the section(s) of this template that are relevant to your *current submission*.

Definitions:

Deferral – A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.

Full Waiver – On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information **MUST** be included in the pediatric use section of labeling.

Partial Waiver – FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.

Pediatric Assessment – The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.

Pediatric Plan – A pediatric plan is the applicant’s statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.

Pediatric Population/Patient- 21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

PREA Pediatric Record/Pediatric Page – The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ***active ingredient(s) (includes new combination);*** ***indication(s);*** ***dosage form;*** ***dosing regimen; or*** ***route of administration?***

Did the sponsor submit an Agreed iPSP? Yes ***No***

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes ***No***

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ***No***

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ***No***

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes ***No***

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.***
- Pediatric Record***

1. Pediatric age group(s) to be waived.

The Applicant proposed and the Agency agreed with the following:

- a partial waiver for patients from birth to < 6 years of age.

2. Reason(s) for waiving pediatric assessment requirements (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.***)

- Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.
- The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
- The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
- Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (***This reason is for***

Partial Waivers Only)

3. Provide justification for Waiver:

The Applicant is seeking a waiver for conducting a pediatric assessment in age groups <6 years of age based predominantly on the lack of prevalence of IBS-d in the very young patient population. The actual incidence rate of IBS in the pediatric population is reported to occur in 0.2% of children from birth to age 12 years, with small epidemiologic studies suggest IBS-c is the most prevalent subtype seen in children. The diagnosis of IBS is based on the presence of abdominal symptoms, making diagnosis in young pediatric patients difficult. In fact, the Rome criteria which are used for diagnosis, contains no IBS criteria for children < 4 years of age.

In addition, while eluxadoline has low oral bioavailability, it has mu opioid agonist activity. Other antimotility agents (eg, loperamide) with mu opioid agonist activity, are generally not recommended for use in young children and infants due to the potential for central nervous system side effects and the theoretical possibility of respiratory depression.

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:

The Review Division agrees with the proposed language for Section 8.4 of the label: Safety and effectiveness in pediatric patients have not been established.

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis

adjunctive treatment of major depressive disorder

age-related macular degeneration

Alzheimer's disease

amyloidosis

amyotrophic lateral sclerosis

androgenic alopecia

atherosclerotic cardiovascular disease

autosomal dominant polycystic kidney disease (ADPKD)

benign monoclonal gammopathy

benign prostatic hyperplasia

cancer:

 basal cell and squamous cell skin cancer

 bladder

 breast

 cervical

 colorectal

 endometrial

 esophageal

cancer (continued):

 follicular lymphoma

 gastric

 hairy cell leukemia

 hepatocellular

 indolent non-Hodgkin lymphoma

 lung (small & non-small cell)

 multiple myeloma

 oropharynx (squamous cell)

 ovarian (non-germ cell)

 pancreatic

 prostate

 refractory advanced melanoma

 renal cell

 uterine

chronic lymphocytic leukemia

chronic obstructive pulmonary disease

cryoglobulinemia

diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)
dry eye syndrome (keratoconjunctivitis sicca)
erectile dysfunction
essential thrombocytosis
Huntington's chorea
infertility & reproductive technology
ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke
memory loss
menopause and perimenopausal disorders
mesothelioma
myelodysplasia
myelofibrosis & myeloproliferative disorders
osteoarthritis
overactive bladder
Parkinson's disease
paroxysmal nocturnal hemoglobinuria
plasma cells and antibody production disorders
polycythemia vera
postmenopausal osteoporosis
prevention of stroke and systemic embolic events in atrial fibrillation

psoriatic arthritis
reduction of thrombotic cardiovascular events in patients with coronary artery disease
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
retinal vein occlusions
stress urinary incontinence
temporary improvement in the appearance of caudal lines
treatment of incompetent great saphenous veins and varicosities
type 2 diabetic nephropathy
vascular dementia/vascular cognitive disorder/impairment

DEFERRAL REQUEST

Please attach:

Pediatric Record

1. Age groups included in the deferral request:

The Applicant proposed and the Agency agreed with the following:

- a deferral for patients from ≥ 6 years to 17 and 11 months of age.

2. Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:

The Division proposes a partial waiver from birth to < 6 years of age.

3. Reason/s for requesting deferral of pediatric studies in pediatric patients with disease: *(Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.)*

Adult studies are completed and ready for approval and pediatric studies should be delayed until determination of possible scheduling assessment of eluxadoline

4. Provide projected date for the submission of the pediatric assessment (deferral date):

All studies are projected to be completed by October 2026 with a plan for pediatric sNDA submission in January 2027.

5. Did applicant provide certification of grounds for deferring assessments? Yes No

6. Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time? Yes No

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. Has a pediatric plan been submitted to the Agency? Yes No
2. Does the division agree with the sponsor's plan? Yes No
3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)? Yes No
 - a. Protocol Submission: Phase 2 Study: 01Jan2016, Phase 3 Study: 31Jul2019, Open-label Safety Study: 31Jul2019
 - b. Study Completion: Phase 2 Study: 15May2019, Phase 3 Study: 15Jul2025, Open-label Safety Study: 15Jul2026
 - c. Study Submission: Phase 2 Study: 15Aug2019, Phase 3 Study: 15Oct2025, Open-label Safety Study: 15Oct2026
4. Has a Written Request been issued? Yes No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)
5. Has a PPSR been submitted? Yes No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design:

- Study 1: A Randomized, Double-Blind, Dose-Ranging Study to Evaluate the Safety and Effectiveness of Eluxadoline in Pediatric Subjects (Aged 6 to 17 years) With Diarrhea-Predominant Irritable Bowel Syndrome
- Study 2: A Randomized, Double-Blind Study to Confinn the Safety and Effectiveness of Eluxadoline in Pediatric Subjects (Aged 6 to 17 years) With Diarrhea-Predominant Irritable Bowel Syndrome
- Study 3: An Open-Label Safety Study of Eluxadoline in Pediatric Subjects (Aged 6-17 Years) With Diarrhea-Predominant Irritable Bowel Syndrome

Nonclinical Studies:

No further nonclinical studies are proposed.

- The Sponsor completed a 1-month oral rat juvenile toxicity study. Similar to results from 6-month studies in adult rats, the juvenile study showed no signs of toxicity in juvenile rats and the NOAEL was the highest dose tested, 1500 mg/kg/day.

- Segment 1-3 reproductive studies did not demonstrate any negative effects on reproductive performance, pregnancy parameters, or fetal development.

Clinical Studies:

Age group and population (indication) in which study will be performed:

The population will be the same for all 3 studies in the Sponsor's pediatric plan and will include patients aged 6 to 17 years and 11 months of age with a diagnosis of IBS with a subtype of diarrhea defined by the Rome III criteria.

Number of patients to be studied or power of study to be achieved:

Study 1: [REDACTED] (b) (4)

Study 2: [REDACTED] (b) (4)

Entry criteria:

The entry criteria for the Phase 2 Dose-ranging study and the phase 3 confirmatory trial are identical and listed below. Patients who complete the phase 3 confirmatory trial will be eligible for the open-label extension study.

Entry Criteria: Male and female subjects meeting with the following criteria:

1. Subject is 6 to 17 years 11 months of age.
2. Subject has a diagnosis of IBS with a subtype of diarrhea defined by the Rome III criteria as loose (mushy) or watery stools \geq 25% and hard or lumpy stools $<$ 25% of bowel movements.
3. Subject has an average of worst abdominal pain scores in the past 24 hours of $>$ 3.0 on the Wong-Baker FACES Pain Rating Scale over the week prior to randomization.
4. Subject has completed the electronic diary on at least 5 of the 7 days during the week prior to randomization AND at least 10 of the 14 days during the 2 weeks prior to randomization.
5. Subject or guardian must sign an informed consent document before the initiation of any study-related procedures indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.
6. Subject has no history of or current evidence of inflammatory GI disorders based on results of fecal calprotectin, c-reactive protein, and erythrocyte sedimentation rate tests.
7. Subject has no history of or current evidence of blood in the stool.
8. Subject has no history of or current evidence of celiac disease based on results of celiac panel tests.
9. Subject has no history of or current evidence of lactose intolerance.
10. Subject has no current evidence of a microbiologically documented lower gastrointestinal infection.
11. Subject has not had a cholecystectomy.

Clinical endpoints:

Study 1: Phase 2 Dose Ranging Study: [REDACTED] (b) (4)

Study 2: Phase 3 Confirmatory Study: [REDACTED] (b) (4)

Study 3: Open-Label Safety Study: [REDACTED] (b) (4)

Timing of assessments:

Study 2:

(b) (4)

Statistical information (statistical analyses of the data to be performed):

Study 1: Phase 2 dose-ranging study:

(b) (4)

Study 2: Phase 3 confirmatory study:

(b) (4)

Division comments on product safety:

Are there any safety concerns currently being assessed? Yes No

Pancreatitis and reversible hepatobiliary spasm events, primarily associated with sphincter of Oddi spasm, were reported in the eluxadoline adult clinical development program.

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? Yes No

Will a DSMB be required? Yes No

Other comments:

Division comments on product efficacy:

If approved for the adult population, this product is effective for the treatment of irritable bowel syndrome with diarrhea (IBS-D). Efficacy and safety in the pediatric population will need to be determined.

Division comments on sponsor proposal to satisfy PREA:

The Sponsor's general pediatric plan, including partial waiver and deferral timeline, is acceptable.

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/s/

JENNIFER S SARCHET
03/04/2015



NDA 206940

MEETING REQUEST GRANTED

Furiex Pharmaceuticals, Inc.
Attention: Michelle P. Usher, RAC
Executive Director, Regulatory Affairs
3900 Paramount Parkway Suite 150
Morrisville, North Carolina 27560

Dear Ms. Usher:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eluxadoline.

We also refer to your January 12, 2015, correspondence requesting a meeting to discuss questions and findings of the Agency's Controlled Substance Staff. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The meeting is scheduled as follows:

Date: February 25, 2015
Time: 3:00 pm – 4:00 pm ET
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Invited CDER Participants:

Julie Beitz, M.D., Director, Office of Drug Evaluation III

Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)

Dragos Roman, M.D., Acting Deputy Director, DGIEP

Andrew E. Mulberg, M.D., Acting Associate Director, Rare Diseases Program, Division Deputy Director, DGIEP

Joyce Korvick, M.D., M.P.H., Deputy Director for Safety, DGIEP

Ruyi He, M.D., DGIEP, Medical Team Leader, DGIEP

Laurie Muldowney, M.D., Medical Officer, DGIEP

Michael Klein, Ph. D., Director, Controlled Substance Staff Team Leader

Alan Trachtenberg, M.D., Medical Officer, Controlled Substance Staff Reviewer

Silvia N. Calderon, Ph.D., Team Leader Pharmacology, Controlled Substance Staff

Jennifer Sarchet RN, BSN, MSHA, Regulatory Project Manager, DGIEP

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

Please e-mail me any updates to your attendees at jennifer.sarchet@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Jennifer Sarchet at 240-402-4275.

Please refer to the following link for visiting the White Oak Campus:

<http://www.fda.gov/aboutfda/workingatfda/buildingsandfacilities/whiteoakcampusinformation/cm241748.htm>

Submit background information for the meeting (three paper copies or one electronic copy to the application) at least 1 month prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by January 25, 2015, we may cancel or reschedule the meeting.

If you have any questions, call me, Jennifer Sarchet Regulatory Project Manager at 240-402-4275.

Sincerely,

{See appended electronic signature page}

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

JENNIFER S SARCHET
02/24/2015

Sarchet, Jennifer

From: Sarchet, Jennifer
Sent: Tuesday, February 17, 2015 2:32 PM
To: 'Michelle Usher'
Subject: NDA 206940; eluxadoline; Information Request 2-17-2015

Michelle,

Please refer to NDA 206940; eluxadoline. We have the following information request and request a response as soon as possible.

- Explain your rationale for including a subgroup analysis by age, where patients < 65 years of age are subdivided into 2 age groups, those between 18 and 40 and those between 41 and 64 years of age.
- Provide a subgroup analysis by age for the primary endpoint, i.e., CR response and also each component separately for Studies IBS-3001 and IBS-3002, where the subgroups are defined as patients < 65 and patients ≥ 65 years of age only.
- Provide baseline IBS disease characteristics for IBS-3001 and IBS-3002, presented separately by age 18 to 40 years, 41 to 64 years, and ≥ 65 years.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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/s/

JENNIFER S SARCHET
02/17/2015

Sarchet, Jennifer

From: Sarchet, Jennifer
Sent: Tuesday, February 17, 2015 10:46 AM
To: 'Michelle Usher'
Subject: NDA 206940; eluxadoline; Labeling Information Request

Hello Michelle,

Please refer to NDA 206940; eluxadoline. We recommend the following:

Container Labels:

60 count bottles:

1. As currently displayed, NDC number is denoted as a placeholder (XXXXX-XXXX-XX). Ensure that the NDC product code is different for both strengths.

Sample Packs:

1. As currently displayed, NDC number is denoted as a placeholder (XXXXX-XXXX-XX). Ensure that the NDC product code is different for both strengths.
2. (b) (4) proprietary name, established drug name and strength. Ensure that each unit dose section presents these required information in the event the blister pack is separated.

You can send samples directly to me.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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/s/

JENNIFER S SARCHET
02/17/2015

Sarchet, Jennifer

From: Sarchet, Jennifer
Sent: Thursday, February 12, 2015 1:28 PM
To: 'Michelle Usher'
Subject: NDA 206940; eluxadoline; Clin Pharm Information Request 2-12-2015

Dear Michelle,

Please refer to NDA 206940; eluxadoline. We have the following clinical pharmacology information request. Please respond within three business days.

1. Regarding the potential for eluxadoline to inhibit the metabolism of co-administered drugs that are CYP3A4 substrates due to mechanism-based inhibition, please assess the in vivo relevance of this interaction according to the current “*DRAFT Guidance for Industry Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*” (page 23) found at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf> by calculating R2 values for interactions at the systemic level and in the gut as described below.

$$TDI, R2 = (Kobs + Kdeg) / Kdeg \text{ and } Kobs = \frac{kinact \times [I]}{KI + [I]}$$

[I] can be estimated by the maximal total (free and bound) systemic inhibitor concentration in plasma and the cutoff for R is 1.1. In addition, for CYP3A inhibitors that are dosed orally, [I] should also be estimated by $[I] = I_{gut} = \text{Molar Dose} / 250 \text{ mL}$ and the cutoff for this alternate R is 11. Kdeg is the apparent first order degradation rate constant of the affected enzyme; kinact and KI are maximal inactivation rate constant and apparent inactivation constant, respectively;

2. Regarding the dataset for study IBS-2001 (ibs2001pkm), please include information on dose, week# and the corresponding concentration. Currently, in the dataset that you have submitted, you only provide concentration values with no dose and week information or only dose information without the concentration.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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/s/

JENNIFER S SARCHET
02/12/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206940

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Furiex Pharmaceuticals, Inc.
3900 Paramount Parkway, Suite 150
Morrisville, NC 27560

ATTENTION: Michelle P. Usher, RAC
Executive Director, Regulatory Affairs

Dear Ms. Usher:

Please refer to your New Drug Application (NDA) dated June 26, 2014, received June 27, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eluxadoline Tablets, 75 mg and 100 mg.

We also refer to your correspondence, dated and received December 23, 2014, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:



Please note that the Federal Food Drug and Cosmetic Act (FD&C Act) provides that labeling or advertising can misbrand a product if misleading representations are made (See 21 U.S.C. 321(n)). The FD&C Act also provides that a drug is misbranded if its labeling is false or misleading in any particular (21 USC 352(a)). A proprietary name, which appears in labeling, could result in such misbranding if it is false or misleading, such as by making misrepresentations with respect to safety or efficacy.

We note that you have proposed an alternate proprietary name in your submission dated December 23, 2014. In order to initiate the review of the alternate proprietary name, Viberzi, submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5295. For any other information regarding this application, contact Jennifer Sarchet, Regulatory Project Manager in the Office of New Drugs, at (240) 402-4275.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
02/03/2015

Sarchet, Jennifer

From: Sarchet, Jennifer
Sent: Monday, February 02, 2015 8:35 AM
To: 'Michelle Usher'
Subject: NDA 206940; eluxadoline; Dissolution

Dear Michelle,

Please refer to NDA 206940; eluxadoline. Your proposed dissolution method is reviewed and found acceptable; however, your proposed dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 20 min is too loose based on the mean dissolution data. Therefore, it is not acceptable, and it should be tightened to $Q = \frac{(b)}{(4)}\%$ at 10 minutes.

Submit your agreement response with the revised M32P51 Specification and other related sections to the Agency no later than February 4th, 2015.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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JENNIFER S SARCHET
02/02/2015

Sarchet, Jennifer

From: Sarchet, Jennifer
Sent: Wednesday, January 28, 2015 4:20 PM
To: 'Michelle Usher'
Subject: NDA 206940; eluxadoline; January 27, 2015 Label
Attachments: Current Label 1-27-2015 NDA 206940; eluxadoline.doc; Current Label 1-27-2015 NDA 206940; eluxadoline.pdf

Importance: High

Michelle,

Please refer to NDA 206940; eluxadoline. Attached you will find the current Prescribing Information (PI) in both a PDF and word version. Please submit both a redlined (track changes) word version and a clean word version of the PI by February 18, 2015.

Please let me know if you have any questions.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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25 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JENNIFER S SARCHET
01/29/2015

From: [Sarchet, Jennifer](#)
To: "Michelle Usher"
Subject: NDA 206940; eluxadoline 1-16-2015 Stats Information Request
Date: Friday, January 16, 2015 4:42:05 PM

Dear Michelle,

Please refer to NDA 206940; eluxadoline. We have the following statistical information request. We request a response by Friday, January 30, 2015.

For both Studies 3001 and 3002, please perform per-protocol analyses by removing all patients with protocol violations for the primary efficacy endpoint and secondary endpoints.

Please let me know if you have any questions.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
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JENNIFER S SARCHET
01/16/2015

From: [Sarchet, Jennifer](#)
To: "Michelle Usher"
Subject: NDA 206940; eluxadoline; 1/16/2015 Clinical Information Request
Date: Friday, January 16, 2015 4:16:55 PM

Dear Michelle,

Please refer to NDA 206940; eluxadoline. We have the following information request and appreciate your response as soon as possible.

1. Provide a summary of abdominal pain adverse events from pooled Phase 2 and 3 studies, including a breakdown of the time course of the initial reporting of symptoms (as provided in your 12 January 2015 submission) but use a broad search of MedDRA terms for abdominal pain including abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, and abdominal distension.
2. Provide an analysis of adverse events in the gastrointestinal disorders SOC, in the subset of patients who used loperamide rescue medication, including an analysis of SAEs, as well as AEs leading to treatment discontinuation. As possible, please analyze the timing of these AEs in relationship to loperamide rescue medication use.
3. ISS Amendment Tables 2.69 and 2.70 include analyses of IVRS-Confirmed Constipation by Quarter for the pooled phase 2 and 3 population. Please clarify which patients continued IVRS reporting during the 3rd Quarter. It is our understanding the IVRS recording continued only through Week 26.

As always, please let me know if you have any questions.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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/s/

JENNIFER S SARCHET
01/16/2015



NDA 206940

MID-CYCLE COMMUNICATION

Furiex Pharmaceuticals, Inc.
Attention: Michelle P. Usher, RAC
Executive Director, Regulatory Affairs
3900 Paramount Parkway Suite 150
Morrisville, North Carolina 27560

Dear Ms. Usher:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for eluxadoline, 100 mg tablets.

We also refer to the teleconference between representatives of your firm and the FDA on December 10, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call LCDR Jennifer Sarchet, Regulatory Project Manager, at 240-402-4275.

Sincerely,

{See appended electronic signature page}

Jennifer Sarchet RN, BSN, MSHC
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: December 10, 2014

Application Number: 206940
Product Name: Eluxadoline
Indication: Treatment of diarrhea and abdominal pain in men and women with diarrhea predominant irritable bowel syndrome (IBS-d)
Applicant Name: Furiex Pharmaceuticals, Inc.

Meeting Chair: Ruyi He, M.D.
Meeting Recorder: Jennifer Sarchet, RPM

FDA ATTENDEES

Julie Beitz, M.D., Director, Office of Drug Evaluation III
Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Andrew E. Mulberg, M.D., Deputy Director, DGIEP
Joyce Korvick, M.D., M.P.H., Deputy Director for Safety, DGIEP
Ruyi He, M.D., DGIEP
Laurie Muldowney, M.D., Medical Officer, DGIEP
Sue-Chih Lee, Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3
Dilara Jappara, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3
Marie Kowblansky, Ph.D., CMC Lead, Office of New Drug Quality Assessment
Tapash Ghosh, Ph.D., Reviewer, Office of Clinical Pharmacology
Mike Welch, Ph.D., Deputy Director, Division of Biometrics III
Yeh-Fong Chen, Ph.D., Statistical Team Leader, Division of Biometrics III
Jamie Wilkins Parker, MD, OSE/DRISK, Team Leader
Nyedra Booker, M.D., OSE/DRISK, Reviewer
Michael Klein, Controlled Substance Staff Team Leader
Alan Trachtenberg, Controlled Substance Staff Reviewer
Kelly Richards, RN, BSN, MSN, Regulatory Project Manager, DGIEP
Jennifer Sarchet RN, BSN, MSHA, Regulatory Project Manager, DGIEP

Furiex Pharmaceuticals, Inc, a subsidiary of Actavis plc

Paul Covington, M.D.	Senior Vice President, Clinical Development & Operations
Gail McIntyre, Ph.D.	Senior Vice President, Research
Mike Davenport, Ph.D.	Executive Director, Clinical Pharmacology & Biostatistics
Scott Dove, Ph.D.	Executive Director, Clinical Operations
Michelle Usher	Executive Director, Regulatory Affairs
Lisa Turner, R.Ph.	Executive Director, Clinical Operations

David Andrae, Ph.D.	Senior Director, Biostatistics & Psychometrics
Tim Costello, Ph.D.	Senior Director, Chemistry
Rocio Lopez, Ph.D.	Director, Early Drug Development

Forest Laboratories , a subsidiary of Actavis plc

Steven Shiff, MD	Executive Director, Clinical Development, Therapeutic Area Head, GI
Darren Weissman, MD	Director, Pharmacovigilance and Risk Management, Global Drug Safety
Kathleen Waldron, MBA	Senior Director, Regulatory Affairs
Ramesh Boinpally, PhD	Fellow, Clinical Pharmacology

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

CLINICAL:

- Discuss the significance of the apparent imbalance of adverse events of abdominal pain in the eluxadoline treatment arms compared to placebo in the context of both efficacy and safety.
- Discuss the feasibility of marketing the 75 mg dose as an alternative to the 100 mg dose in patients who cannot tolerate the 100 mg dose.

Meeting Discussion: Furiex expressed an understanding and would explore the potential for marketing both 75 mg and 100 mg. They clarified that they did not have PK data at the 75 mg dose.

3.0 INFORMATION REQUESTS

Information Request #1 (Clinical/Statistics): (Sent December 4, 2014): Provide the rationale for including risk factors for sphincter of Oddi spasm and pancreatitis as contraindications for eluxadoline use. A drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Please refer to the Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed

Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format.

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065010.htm>

For Study IBS-3002, provide a summary of adverse events which occurred during the single-blinded withdrawal period and which could indicate withdrawal potential (e.g., anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and hallucinations). This summary should exclude the 25 patients who continued to take active study drug during the 4-week single-blind withdrawal period due to a systematic error in the IVR/IWR system.

We note that there are more than 100 patients in Study 3001 and more than 50 patients in Study 3002 who failed inclusion/exclusion criteria but were randomized and treated. Please provide the USUBJID for these patients and perform a sensitivity analysis for the primary endpoint separately for each study, excluding these patients.

Meeting Discussion: No meeting discussion occurred.

Information Request #2 (Clinical Pharmacology): Please provide tabulated safety data for the following subgroups of patients from the phase 2/3 studies. Include individual data on patient ID and the associated adverse events.

- Patients with hepatic impairment (categorized as mild, moderate and severe)
- Patients with renal impairment (categorized as mild, moderate and severe)
- Patients who were taking concomitant OAPT1B1 inhibitors such as cyclosporine.

Meeting Discussion: Furiex clarified that they provided data on baseline elevated bilirubin and baseline ALT as agreed upon during the pre-NDA meeting. OAPT1B1 haplotypes were also provided in the pre-NDA meeting package. Furiex provided the location of this data in the ISS. FDA asked for safety data from subjects who were taking OAPT1B1 inhibitors. Furiex will provide a list of relevant drugs for agreement prior to providing the safety analysis. Furiex has already provided summaries for hepatic and renal impairments in the ISS. They will provide line listings for both of the subgroups.

Information Request #3 (Chemistry, Manufacturing and Controls):

Drug substance

1. Please provide peak purity data for samples subjected to forced degradation studies using the assay HPLC method (Method #: 5192) that will be used to release your drug substance.
2. For validation of intermediate precision of the HPLC method (Method #: 5192) used for assay and related substances of the drug substance, please provide complete

validation results obtained in both [REDACTED] (b) (4).

3. The evaluation of the intermediate precision of the GC method (Method #: 5200) used for analysis of residual solvents in the drug substance is missing; please provide validation results for the intermediate precision of the method.
4. Please provide batch information including source and certificate of analysis for the reference standard of impurity [REDACTED] (b) (4) that was used in the HPLC method (Method #: 5192) validation.
5. Provide a retest period with supportive stability data for Eluxadoline reference standard.
6. Please include an appropriate test in your drug substance specification to ensure the correct [REDACTED] (b) (4) of the drug substance.

Drug product

1. Since the HPLC methods for content uniformity and assay provided in the validation report (FRX-AR-015-0412-R0) are different, please provide the validation report for the HPLC method used for content uniformity testing (Method #: 930031).
2. Your validation report for the HPLC method (Method #: 930032) used for dissolution testing lacks an evaluation of the accuracy of the method. Please address this omission.
3. Please clarify what the package configuration of the physician sample will be. Also, confirm that the blister package will conform to child resistant standards required by the Poison Prevention Packaging Act (PPPA).
4. Please provide samples of each packaging configuration you propose to produce.

Meeting Discussion: Furiex stated they had no questions.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.

Meeting Discussion: No meeting discussion occurred.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an AC meeting.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

Late-Cycle Meeting is March 11, 2015 from 9:30 – 10:30 am ET.

7.0 ADDITIONAL COMMENTS: Applicant asked for clarification as to the status of Controlled Substance Staff (CSS) review of the drug and the scheduling of eluxadoline. CSS staff clarified that the drug does have a greater opioid effect than placebo. A full dependence assessment of the drug will be necessary. The FDA asked Furiex to provide a full summary of data on withdrawal. (b) (4)

(b) (4) FDA clarified that we will review the most recent data related to abuse and withdrawal and submit an information request with any additional information that is needed to continue the review.

CSS POST MEETING CLARIFYING AND ADDITIONAL COMMENTS:

1. Eluxadoline binds to the Mu receptor as an agonist and crosses the Blood Brain Barrier. Of the mu agonist opioids indicated primarily for diarrhea, only Loperamide is unscheduled and it does not cross the BBB. In addition, eluxadoline has delta opioid antagonist activity. (b) (4)
(b) (4) However, abuse liability is likely to increase if the oral product is manipulated and the product is taken by injection or insufflation. Scheduling under the Controlled Substances Act (CSA) applies to the activity of the substance, not the drug product.
2. All of the other opioid agonists that cross the BBB are controlled under the CSA:
 - a. Diphenoxylate CII (as the drug substance), or CV when combined with atropine as in Lomotil (as a drug product),
 - b. Opium tincture (laudanum): C II,
 - c. Camphorated opium tincture (paregoric): CIII
3. Eluxadoline self-administration was reinforcing in 5/5 monkeys, one of which died several hours after finishing its last injection sequence. The Sponsor stated that the animal that died was ill. Healthy animals should have been used in the study.
4. In looking at the following from the safety report: Adverse events of euphoric mood (specifically, reporting “feeling drunk”) and somnolence were each observed for only 1 (1.7%) healthy patient with the 1000-mg dose in healthy subjects (Study CPS-1008); However, Study CPS-1006 was a double blind, double dummy crossover comparing oral doses of eluxadoline with placebo and with oxycodone. Adverse events of euphoric mood were reported by 10 (27.8%) of the recreational drug abuser subjects after taking 1000 mg of eluxadoline and by only 2 (5.4%) following their placebo dose. It appears that a significantly higher proportion of recreational abusers (approximately 25 %) got high (euphoric) on drug than got high on placebo (approximately 5%) with a 1000 mg dose, which would not be that difficult to take. We are as concerned about non-patient drug abusers (which is a high risk population) getting high from the drug, as we are about the patients, since the drug abusers are the ones more likely to divert and/or abuse it. If

25% do get euphoric from it, then it may be of concern. If uncontrolled, this sort of non-patient use (abuse) is more likely to occur.

5. From CPS-1006 (oral): “Eluxadoline showed statistically higher scores on the Take Drug Again VAS for eluxadoline 1000 mg at the 24-hour time point. The 300 mg and 1000 mg eluxadoline doses were significantly higher than placebo on Subjective Drug Value (SDV) at 12 hours and 24 hours, though lower than either dose of oxycodone IR at both time points.”
6. On Drug Similarity VAS, while oxycodone IR was identified strongly as an opioid with mean scores of approximately 72 to 75 (on a scale of 0-100) for the 2 doses, mean responses for eluxadoline 300 mg and 1000 mg showed slightly higher scores (mean of 20) relative to placebo (mean of 4).
7. From CPS-1010 (nasal abuse): Statistically significant decreases in pupil diameter were observed following eluxadoline; however, these decreases were less than the decrease observed after either dose of oxycodone. We are submitting these studies to Biostatistics for a full statistical review.

Summary:

8. Overall, there are a variety of measures on which eluxadoline has greater opioid effects than placebo, albeit less than the full Mu agonist oxycodone when taken orally. Other routes of administration for eluxadoline have not been studied for abuse potential in humans.
9. This, plus the animal findings that the drug does pass the Blood Brain Barrier from systemic circulation, does suggest that Intravenous administration of the drug substance would likely be reinforcing to opioid abusers.
10. Furiex needs to perform a full dependence assessment of the drug. We would like Furiex to tabulate all abuse-relevant Adverse Events from all their clinical trials, broken down by study, by Phase 1, 2, and 3, by subject type, by event and by dose; also by duration after dosing for both reinforcing and dependence-related events. Please refer to FDA’s *DRAFT GUIDANCE for Industry Assessment of Abuse Potential of Drugs* <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf>

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JENNIFER S SARCHET
01/09/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206940

**PROPRIETARY NAME REQUEST
ACKNOWLEDGEMENT/WITHDRAWAL**

Furiex Pharmaceuticals, Inc.
3900 Paramount Parkway
Suite 150
Morrisville, NC 27560

ATTENTION: Michelle P. Usher, RAC
Executive Director, Regulatory Affairs

Dear Ms. Usher:

Please refer to your New Drug Application (NDA) dated June 26, 2014, received June 27, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eluxadoline Tablets, 75 mg and 100 mg.

We also refer to your correspondence, dated and received December 23, 2014, notifying us that you are withdrawing your request for a review of the proposed proprietary name, (b) (4) is considered withdrawn as of December 23, 2014.

We further refer to your correspondence, dated and received December 23, 2014, requesting review of your proposed proprietary name, (b) (4). The user fee goal date for (b) (4) is March 23, 2015.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5295. For any other information regarding this application, contact Jennifer Sarchet, Regulatory Project Manager in the Office of New Drugs, at (240) 402-4275.

Sincerely,

{See appended electronic signature page}

Aleksander Winiarski, Pharm.D.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

ALEKSANDER P WINIARSKI
12/31/2014

From: [Sarchet, Jennifer](#)
To: "Michelle Usher"
Subject: NDA 206940; Eluxadoline; Clin Pharm Information Request 12/24/2014
Date: Wednesday, December 24, 2014 10:30:00 AM

Hello Michelle,

Please refer to NDA 206940; Eluxadoline. We have the following information request that you respond within three business days.

1. You have conducted your protein binding study at 200 and 2000 ng/mL while the expected therapeutic concentration of eluxadoline (JNJ-27018966) in human subject at the clinical dose of 100 mg dose is 2-3 ng/mL. Although no concentration dependent change in human binding was observed between 200 and 200 ng/mL, we are uncertain that this concentration independency in protein binding can be extrapolated to 2 ng/mL. Please provide justification for your choice of concentration in your protein binding study.
2. Please clarify if you have evaluated the induction potential of CYP2B6 by eluxadoline (JNJ-27018966).
3. Please clarify if you have evaluated the inhibition potential of CYP2C8 by eluxadoline (JNJ-27018966).

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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JENNIFER S SARCHET
12/24/2014

From: [Sarchet, Jennifer](#)
To: "Michelle Usher"
Subject: NDA 206940; (b) (4) (eluxadoline); Information Request
Date: Thursday, December 04, 2014 2:21:49 PM

Dear Michelle,

Please refer to NDA 206940; (b) (4) (eluxadoline). We have the below information request. We appreciate your timely response as soon as possible.

- Provide a rationale for inclusion of risk factors for sphincter of Oddi spasm and pancreatitis as contraindications for eluxadoline use. A drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. For observed adverse reactions, the risk of the adverse reaction in the clinical situation to which the contraindication, based on both likelihood and severity of the adverse reaction, outweighs any potential benefit to any patient. Please refer to the Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format.
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065010.htm>
- For Study IBS-3002, provide a summary of adverse events which occurred during the single-blinded withdrawal period and which could indicate withdrawal potential (e.g., anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and hallucinations). This summary should exclude the 25 patients who continued to take active study drug during the 4-week single-blind withdrawal period due to a systematic error in the IVR/IWR system.
- We note that there are more than 100 patients in Study 3001 and more than 50 patients in Study 3002 who failed inclusion/exclusion criteria but were randomized and treated. Please provide the USUBJID for these patients and perform a sensitivity analysis for the primary endpoint separately for each study, excluding these patients.

As always please let me know if you have any questions.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
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/s/

JENNIFER S SARCHET
12/04/2014

From: [Sarchet, Jennifer](#)
To: "Michelle Usher"
Subject: NDA 206940; (b) (4) (eluxadoline); Information Request
Date: Monday, December 01, 2014 6:45:57 AM

Dear Michelle,

Please refer to NDA 206940; (b) (4) (eluxadoline). Please respond to following information request by COB on Wednesday, December 3, 2014.

1. You have evaluated the potential metabolism of eluxadoline (JNJ-27018966) in human hepatocytes (study FK5826), human intestinal microsomes (study FK5944), microsome and S9 (study 27018966EDI1003). Please provide data to support that these test systems were viable in regards to various phase I and phase II enzymes, including the results for both positive controls and negative controls.
2. In the mass balance study (study 27018966EDI1003), it is not clear if you have conducted metabolic profiling of JNJ-27018966 using fecal samples. If so, please provide the results.
3. You have indicated that no metabolite was detected in the samples obtained from the mass balance study (study 27018966EDI1003). In addition, you have also evaluated the metabolic profiling using samples obtained following administration of 1000 mg single dose in study 27018966EDI1001. It is not clear what the assay sensitivities were in these metabolic profiling studies. Please indicate the assay sensitivity for both studies.
4. Please clarify if you have any data to estimate the absolute bioavailability of eluxadoline following oral administration in humans? (In animal studies, the absolute bioavailability was estimated to be 0.2%). Without this information, one cannot determine if renal excretion is a major elimination pathway or not.)

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

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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/s/

JENNIFER S SARCHET
12/01/2014

From: [Sarchet, Jennifer](#)
To: "Michelle Usher"
Subject: NDA 206940; (b) (4) (eluxadoline); Information Request
Date: Tuesday, November 25, 2014 3:35:09 PM

Dear Michelle,

Please refer to NDA 206940; (b) (4) (eluxadoline). We have the following information request. We request a response, if possible by COB on December 2, 2014. Please provide a summary table showing treatment exposure by time interval for the pooled analysis phase 2 and phase 3 population, including only 75mg, 100mg, and placebo BID as follows:

	Eluxadoline 75 mg BID (N = 807) n (%)	Eluxadoline 100mg BID (N = 1032) n (%)	Placebo BID (N = 975) n (%)
Treatment duration			
≥ 1 day			
≥ 1 week			
≥ 4 weeks			
≥ 12 weeks			
≥ 26 weeks			
≥ 52 weeks			

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
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/s/

JENNIFER S SARCHET
11/25/2014

From: [Sarchet, Jennifer](#)
To: "Michelle Usher"
Subject: NDA 206940; (b) (4) (eluxadoline); Major Amendment Letter and Label
Date: Friday, November 21, 2014 3:34:52 PM
Attachments: [Sponsor Copy DARRTS Signed Copy Review Extension- Major Amendment \(COR-NDAEXTEND-01\)\(COR-BLAEXTEND-01\).pdf](#)
[Current Label NDA 206940 \(Combined FDA and Sponsor\) Comments.11.21.14.doc](#)
[Current Label NDA 206940 \(Combined FDA and Sponsor\) Comments.11.21.14.pdf](#)

Dear Michelle,

Please refer to NDA 206940; (b) (4) (eluxadoline). Thank you for the revised Prescribing Information (PI) for (b) (4) submitted on October 24, 2014, which contained revisions in response to our comments in the Day 74 letter dated September 9, 2014. In general, your proposed revisions have addressed our comments and we have accepted your edits. However, we would like to request some additional edits (track changes) and have also included some new comments (balloons in the margin), as indicated in the attached version.

Please note that all comments/edits proposed and accepted to date are meant to address labeling regulations, guidances and best practices for format and high-level content. Additional more in-depth edits to the content of the PI will be proposed as the review team completes their scientific review of the submission.

Please submit both a redlined (track changes) Word version and a clean Word version of the PI by December 12, 2014.

Attached you will also find a courtesy copy of the Review Extension – Major Amendment letter. You should receive the original in the mail soon.

As always, if you have any questions please let me know.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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26 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JENNIFER S SARCHET
11/21/2014



NDA 206940

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Furiex Pharmaceuticals, Inc.
Attention: Michelle P. Usher, RAC
Executive Director, Regulatory Affairs
3900 Paramount Parkway Suite 150
Morrisville, North Carolina 27560

Dear Ms. Usher:

Please refer to your New Drug Application (NDA) dated June 26, 2014, received June 27, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) (eluxadoline), 100 mg tablets.

On October 23, 2014, we received your October 23, 2014, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is May 27, 2015.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the PDUFA Reauthorization Performance Goals and Procedures – Fiscal Years 2013 through 2017. If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 27, 2015.

Furthermore, the new planned date for our internal mid-cycle review meeting is December 4, 2014.

If you have any questions, call LCDR Jennifer Sarchet, Regulatory Project Manager, at 240-402-4275.

Sincerely,

{See appended electronic signature page}

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

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/s/

BRIAN K STRONGIN
11/21/2014

From: [Sarchet, Jennifer](#)
To: "Michelle Usher"
Subject: NDA 206940; (b) (4) (eluxadoline): Statistical Information Request
Date: Thursday, October 09, 2014 11:17:59 AM

Dear Michelle,

Please refer to NDA 206940; (b) (4) (eluxadoline). We have the following statistical information request.

For both Phase 3 studies, we have tried to confirm your analysis results for the primary endpoint using patients' raw data and the criteria you described in the protocol. However, we have produced different responder status for the following patients.

Please provide detailed explanation about how you determined the following patients' composite response status using their raw data in all visits.

- For Study 3001: Subjects No. 0640012, 2220003, 2960006, 3430002, 3590025, 4180006 and 4530001
- For Study 3002: Subject No. 5040005, 5340005, 5660003, 6890004, 7450023, 9180031, 5410015, 5410023, 6130008, 6160002, 6180004, 6210011, 6480001, 6650004, 6780015, 5910014 and 7670004

Your response is appreciated as soon as possible to help continue our review. Upon submitting your official response to the NDA, please also e-mail me an exact electronic copy of the submission.

As always, please let me know if you have any questions.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

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JENNIFER S SARCHET
10/09/2014

From: [Kozeli, Devi](#)
To: [Sarchet, Jennifer](#)
Subject: RE: NDA 206940; (b) (4) Information Request
Date: Thursday, September 25, 2014 1:40:47 PM

Hi Jennifer,

It looks like we got what we need.

Thanks for the follow up.

Devi

Devi Kozeli, RAC
Regulatory Health Project Manager
Assistant to the Division Director
QT Interdisciplinary Review Team
Division of Cardiovascular and Renal Products
CDER / OND / ODE1
U.S. Food and Drug Administration
10903 New Hampshire Avenue, WO-22, Suite 4183
Silver Spring, MD 20993-0002

Phone: (301) 796-1128

Fax: (301) 796-9841

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From: Sarchet, Jennifer
Sent: Wednesday, September 24, 2014 10:10 AM
To: Kozeli, Devi
Subject: FW: NDA 206940; (b) (4) Information Request

Hello Devi,

Please see the sponsor's e-mail below and the attached spreadsheet for NDA 206940; (b) (4) Please let me know how you would like to proceed.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products
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From: Michelle Usher [<mailto:Michelle.Usher@furiex.com>]
Sent: Wednesday, September 24, 2014 10:02 AM
To: Sarchet, Jennifer
Subject: RE: NDA 206940; (b) (4) Information Request

Hi Jennifer,

The datasets in ECG Warehouse contain the variables "SID" and "USUBJID", but "SID" is not the Subject ID it is Screen ID while "USUBJID" is the USUBJID that maps to the clinical datasets. Attached is an Excel spreadsheet mapping the SID (SCREENID) variable to PT (where PT is the SUBJID found in the ADSL dataset). The mapping of the variables USUBJID, SUBJID and RANDID exist already in the ADSL dataset for Study CPS-1008 contained in the NDA.

Please let me know if this adequately answers your question or if you need further information. Also, let me know if I need to formally submit this to the NDA, converting the Excel file to an xpt format.

Thanks,
Michelle

From: Sarchet, Jennifer [<mailto:Jennifer.Sarchet@fda.hhs.gov>]
Sent: Tuesday, September 23, 2014 2:17 PM
To: Michelle Usher
Subject: NDA 206940; (b) (4) Information Request

Michelle,

Please refer to NDA 206940; (b) (4) We have the following information request. Please submit a subject map file to match USUBJID in clinical datasets with those Subject ID in ECG Warehouse for Study

CPS-1008. Your prompt attention to this request is appreciated. In addition, please e-mail me when you have submitted this information to application.

If you have any questions, please let me know.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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/s/

JENNIFER S SARCHET
10/09/2014

From: [Sarchet, Jennifer](#)
To: "Michelle Usher"
Subject: RE: NDA 206940; (b) (4)
Date: Thursday, September 18, 2014 8:06:04 AM

Hello Michelle,

For NDA 206940; (b) (4) it is acceptable to submit your returned label from the 74 day letter request in WORD format with the upcoming safety amendment by October 27, 2014. As always, if you have any questions please let me know.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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From: Michelle Usher [mailto:Michelle.Usher@furiex.com]
Sent: Friday, September 12, 2014 11:06 AM
To: Sarchet, Jennifer
Subject: RE: NDA 206940

Hi Jennifer,

I am sorry to keep bothering you about this, but do you have an update for me on the final Day 74 letter?

Since we have not received it yet , we are not fully aware of what the specific labeling comments

are, therefore, we are asking for an extension for supplying the label responses. The extension should be reflective of the number of days the final Day 74 letter was delayed. I also would like to ask that upon our response to the Day 74 letter, if we can supply our revised label without SPL and provide it in Word format only?

Also, please be aware that we had planned on submitting a revised label in Word and SPL format with the safety amendment (in October). Therefore, alternatively we could hold off with the label responses and include them with the safety amendment? Otherwise, we are happy to provide you the label in response to the D74 as requested, but note that another labeling amendment will follow (perhaps even as soon as 2 weeks later) to accommodate the minor updates to AE rates based on the safety amendment.

Can you please confirm that the above is acceptable, including the label response extension as well as the status of the final letter?

Thanks,
Michelle

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/s/

JENNIFER S SARCHET
09/23/2014

From: [Sarchet, Jennifer](#)
To: "Michelle Usher"
Subject: NDA 206940; (b) (4) (eluxadoline); Information Request
Date: Thursday, September 11, 2014 7:40:09 AM

Dear Ms. Usher,

Please refer to NDA 206940; (b) (4) (eluxadoline). We are reviewing the clinical sections of your submission and have the following comments and information request. We request your prompt written response in order to continue our evaluation of your NDA. Please respond by September 25, 2014. Upon submitting your official response to the NDA, please also e-mail me an exact electronic copy of the submission.

1. Tabulate all patient discontinuations with primary reason listed as "Physician decision: other" for studies IBS-3001 and IBS-3002, separately by study and specific reason listed, in the format shown below:

Reason for discontinuation	Eluxadoline 75 mg BID N = n(%)	Eluxadoline 100 mg BID N = n(%)	Placebo BID N = n(%)	Total N = n(%)
Patient noncompliance				
Etc,				
Total				

2. We note that listings for protocol violations are provided in Module 5, Listings 16.2.2 for studies IBS-3001 and IBS-3002. Please tabulate all protocol violations provided in the data listings for studies IBS-3001 and IBS-3002, separately by study and violation, in the format shown below:

Type of Protocol Violation	Eluxadoline 75 mg BID N = n(%)	Eluxadoline 100 mg BID N = n(%)	Placebo BID N = n(%)	Total N = n(%)
Informed consent issues				
Excluded				

medication taken				
Etc,				
Total				

3. Please provide an updated subject disposition table (Enrolled Set) for study IBS-3001 with your planned protocol amendment.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN, MSHA
 LCDR, U.S. Public Health Service Corps
 Regulatory Project Manager
 Division of Gastroenterology and Inborn Errors Products
 Office of Drug Evaluation III
 CDER/FDA
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JENNIFER S SARCHET
09/11/2014



NDA 206940

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Furiex Pharmaceuticals, Inc.
3900 Paramount Parkway
Suite 150
Morrisville, NC 27560

ATTENTION: Paul S. Covington, M.D.
Senior Vice President, Clinical Development and Operations

Dear Dr. Covington:

Please refer to your New Drug Application (NDA) dated June 26, 2014, received June 27, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eluxadoline Tablets, 75 mg and 100 mg.

We also refer to your correspondence requesting review of your proposed proprietary name, (b) (4). We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your June 26, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Phong Do, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4795. For any other information regarding this application, contact Jennifer Sarchet, Regulatory Project Manager in the Office of New Drugs, at (240) 402-4275.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
09/05/2014



NDA 206940

**METHODS VALIDATION
MATERIALS RECEIVED**

Furiex Pharmaceuticals, Inc.
Attention: Paul S. Covington MD
3900 Paramount Parkway
Suite 150
Morrisville, NC 27560

Dear Paul S. Covington MD:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4)™ and to our August 19, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on August 27, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
08/28/2014



NDA 206940

PRIORITY REVIEW DESIGNATION

Furiex Pharmaceuticals, Inc.
Attention: Michelle Usher, RAC
Executive Director, Regulatory Affairs
3900 Paramount Parkway Suite 150
Morrisville, North Carolina 27560

Dear Ms. Usher:

Please refer to your New Drug Application (NDA) dated June 26, 2014, received June 27, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (eluxadoline).

We also refer to your amendments dated July 18, 2014, August 12, 2014, August 15, 2014, August 19, 2014, and August 22, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is February 27, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 4, 2014.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before September 9, 2014.

If you have any questions, call LCDR Jennifer Sarchet, Regulatory Project Manager, at 240-402-4275.

Sincerely,

{See appended electronic signature page}

Donna Griebel, MD
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DONNA J GRIEBEL
08/27/2014



NDA 206940

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Furiex Pharmaceuticals, Inc.
Attention: Paul S. Covington, MD
3900 Paramount Parkway
Suite 150
Morrisville, NC 27560
FAX: (919) 456-7850

Dear Paul S. Covington, MD:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b)(4)TM (eluxadoline) Tablets.

We will be performing methods validation studies on (b)(4)TM (eluxadoline) Tablets, as described in NDA 206940.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

5192 HPLC method for purity and assay of drug substance
930224 Assay/Related substances and product ID by UPLC

Samples and Reference Standards

500 mg Eluxadoline API
2 x 300 mg Eluxadoline drug reference standard
20 mg (b)(4) impurity if available
50 mg (b)(4) impurity reference standard
60 75-mg (b)(4)TM (eluxadoline) Tablets
60 100-mg (b)(4)TM (eluxadoline) Tablets

Equipment

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
08/19/2014

From: [Sarchet, Jennifer](#)
To: ["Michelle Usher"](#)
Cc: [Barley, Stacy](#)
Subject: NDA 206940; (b) (4) (eluxadoline) tablets; Information Request #2 August 11, 2014
Date: Monday, August 11, 2014 11:39:56 PM

Hello Ms. Usher,

Please refer to NDA 206940; (b) (4) (eluxadoline) tablets. Please see the information request below and provide a response as soon as possible. We are reviewing your submission and have the following comments and requests for information in reference to Protocol 27018966IBS3001 entitled, "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-27018966 in the Treatment of Patients with Diarrhea-Predominant Irritable Bowel Syndrome" and Protocol 27018966IBS3002 entitled, "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-27018966 in the Treatment of Patients with Diarrhea- Predominant Irritable Bowel Syndrome:"

1. To facilitate our understanding of how data were transmitted from the eDiary and prepared for submission to the Agency, please provide a flow diagram and narrative that tracks the course of data generated by the subject through submission in the NDA. Please also include a diagram that tracks the course of the data to the clinical investigator for archiving at the end of the trial. The diagram should identify who was responsible for each step in the process, including description of calculation of the primary endpoint and also specific points in dataflow where an audit trail exists.
2. Provide the location or locations of the documents related to the information request above (e.g. in clinical trial file at sponsor site, at CRO, etc.) and the location of the diary data (e.g. at clinical investigator site, sponsor site, at CRO, etc.).
3. Provide the name of the CRO responsible for the:
 - a. IVRS/IWRS system for the diary data.
 - b. IVRS/IWRS system for the treatment dispensing.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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/s/

JENNIFER S SARCHET
08/11/2014

From: [Sarchet Jennifer](#)
To: "Michelle Usher"
Cc: [Davis Anissa](#); [Barley Stacy](#)
Subject: NDA 206940; (b) (4) (eluxadoline) tablets; Information Request
Date: Friday, August 08, 2014 1:54:13 PM

Hello Ms. Usher,

Please refer to NDA 206940; (b) (4) (eluxadoline) tablets. Please see the clinical pharmacology information request below. Please provide a response for items 1-2 by COB on August 12, 2014. For items 3-7 please provide a response by August 22, 2014.

1. Please submit the full bioanalytical assay validation reports for all bioanalytical methods utilized in this application. If you already have done so, please assist us locating them. Please refer to the following guidance for more information.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf>

We note that you have submitted a validation report for measuring plasma eluxadoline concentration via HPLC-MS/MS by (b) (4) in population PK /PD report, Amendment 1 (dated 02/03/2012) as an attachment 11 (dated June 2010). However, in this validation report, stability of eluxadoline at (b) (4) °C and (b) (4) °C were only established for (b) (4) days. Please provide the long term sample storage stability that cover the duration of time from sample collection to sample analysis.

List of identified bioanalytical method used in the clinical pharmacology studies:

- 1) Plasma eluxadoline concentration via HPLC-MS/MS by (b) (4)
 - 2) Urine eluxadoline concentration via HPLC-MS/MS by (b) (4)
 - 3) Plasma rosuvatin concentration by HPLC-MS/MS by (b) (4)
 - 4) Plasma ethinyl estradiol concentration by HPLC-MS/MS by (b) (4)
 - 5) Plasma norethindrone concentration by HPLC-MS/MS by (b) (4)
 - 6) Plasma eluxadoline concentration with LC-MS/MS by (b) (4)
 - 7) Urine eluxadoline concentration with LC-MS/MS by (b) (4)
2. Please clarify if you have addressed the potential for drug interactions with gastric acid reducing agents as agreed at the Pre-NDA meeting?
 3. We could not locate the POPPK and PK/PD datasets for NDA 206940 (study IBS-2001). Please submit all the datasets, program codes, definition files associated with poppk and pk/pd reports. If you have already submitted, please assist us with the exact location in the EDR. For general expectations for submitting pharmacometric data and models, please refer to <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.
 4. For study EDI-1001, please include the corresponding dose for both the concentration time profile dataset and PK parameter dataset.
 5. Provide supporting evidence that eluxadoline is eliminated primarily by biliary route.
 6. Based on in vitro studies, eluxadoline is substrate for BSEP transporter. Please clarify if you have evaluated the in vivo potential interaction of eluxadoline with BSEP transport.
 7. In order to facilitate our analysis, please put each PK parameters in different columns in PK parameter dataset in all clinical pharmacology studies. In addition, the PK parameter dataset should also include subject ID, treatment, period, and sequence in different columns.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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/s/

JENNIFER S SARCHET
08/08/2014



NDA 206940

NDA ACKNOWLEDGMENT

Furiex Pharmaceuticals
Attention: Paul S. Covington, MD
Senior Vice President, Clinical Development and Operations
3900 Paramount Parkway Suite 150
Morrisville, North Carolina 27560

Dear Dr. Covington:

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

Name of Drug Product: (b) (4) (eluxadoline) tablets, for oral use

Date of Application: June 26, 2014

Date of Receipt: June 27, 2014

Our Reference Number: NDA 206940

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 August 26, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at 240-402-4275.

Sincerely,

{See appended electronic signature page}

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JENNIFER S SARCHET
07/11/2014



IND 079214

MEETING MINUTES

Furiex Pharmaceuticals, Inc.
Attention: Michelle P. Usher, R.A.C.
Executive Director, Regulatory Affairs
3900 Paramount Parkway, Suite 150
Morrisville, NC 27560

Dear Ms. Usher:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for JNJ-27018966 (eluxadoline).

We also refer to the meeting between representatives of your firm and the FDA on April 22, 2014 and your submission dated April 25, 2014. The purpose of the meeting was to discuss and seek FDA concurrence on the acceptability of the data proposed to support the filing of a New Drug Application (NDA) for the marketing approval of eluxadoline.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-5016.

Sincerely,

{See appended electronic signature page}

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
OSI Pre-NDA/BLA Request
Clinical Pharmacology Summary Aid
Furiex's email dated April 17, 2014
Furiex's PowerPoint Presentation received April 21, 2014



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: April 22, 2014; 10:00 a.m. – 11:00 a.m. (EST)
Meeting Location: FDA White Oak Building 22, Room 1309

Application Number: 079214
Product Name: JNJ-27018966 (eluxadoline)
Indication: **Treatment of Diarrhea-predominant Irritable Bowel Syndrome (IBS-d)**

Sponsor/Applicant Name: Furiex Pharmaceuticals, Inc.

Meeting Chair: Dr. Ruyi He
Meeting Recorder: CDR Anissa Davis-Williams

FDA ATTENDEES

Julie Beitz, MD, Director, Office of Drug Evaluation III (ODEIII)
Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Andrew E. Mulberg, M.D., F.A.A.P., C.P.I., Deputy Director, DGIEP
Ruyi He, M.D., Medical Team Leader, DGIEP
Joyce Korvick, M.D., M.P.H., Deputy of Safety, DGIEP
Nancy Snow, M.D., Medical Officer, DGIEP
Insook Kim, Ph.D., Reviewer, Division of Clinical Pharmacology III (DCPIII)
Sushanta Chakder, Ph.D., Supervisory Pharmacologist, DGIEP
Tamal Chakraborti, PhD, Nonclinical Reviewer
Chad J. Reissig, Ph.D., Pharmacologist, Controlled Substance Staff (CSS)
Freda Cooner, Ph.D., Acting Team Leader, Division of Biometrics III
Carlos Mena-Grillasca, R.Ph., Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Matthew J. Barlow, RN, B.S.N., Safety Evaluator, DMEPA
Sharon R. Mills, B.S.N., RN, C.C.R.P., Senior Patient Labeling Reviewer, DMPP
Christian Cao, M.P.A.S., PA-C, Safety Evaluator, Division of Pharmacovigilance 1 (DPV-1)
Nyedra W. Booker, Pharm.D., M.P.H., Risk Management Analyst, Division of Risk Management (DRISK)
CDR Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M., Senior Regulatory Project Manager, DGIEP

EASTERN RESEARCH GROUP ATTENDEES

So Hyun Kim, Independent Assessor

SPONSOR ATTENDEES

Paul Covington, M.D., Senior Vice President, Clinical Development & Operations

Gail McIntyre, Ph.D., Senior Vice President, Research

Scott Dove, Ph.D., Executive Director, Clinical Operations

Michelle Usher, Executive Director, Regulatory Affairs

1.0 BACKGROUND

Eluxadoline's proposed indication is for the treatment of diarrhea and abdominal pain in men and women with diarrhea predominant irritable bowel syndrome (IBS-d).

On January 3, 2014, Furiex Pharmaceuticals, Inc. submitted a preliminary Pre-NDA meeting request to discuss and seek FDA concurrence on the acceptability of the data proposed to support the filing of a New Drug Application (NDA) for the marketing approval of eluxadoline.

On January 7, 2014, the meeting request was granted to occur via face-to-face on April 22, 2014 at the White Oak campus at the Food and Drug Administration in Silver Spring, Maryland.

2.0 DISCUSSION

Questions from Furiex Pharmaceuticals, Inc. (Furiex) are in plain text. The preliminary FDA responses sent to Furiex on April 17, 2014 are in **bold text**. Comments and questions from Furiex on April 17, 2014 are in *italics*. The meeting discussion from April 22, 2014 is in **bold italics**.

2.1 Labeling

Full prescribing information as outlined in the draft (b) (4)™ label has been written based on the nonclinical and clinical development program to date and meets FDA's Physician Labeling Rule (PLR) requirements and associated FDA guidances for format and content, including the 2008 Proposed Rule regarding the content and format of the pregnancy and lactation section of labeling. Additionally the labeling comprises a Medication Guide to ensure proper use of eluxadoline, in order to avoid serious adverse events.

1. Does the FDA agree that the proposed elements of the package insert are acceptable?

FDA Response:

Yes, this seems to be acceptable.

Additional Discussion:

No additional discussion needed

2. Does the FDA agree with our proposed indication statement?

FDA Response:

We cannot agree with your proposed indication statement until we have thoroughly reviewed your NDA.

Additional Discussion:

No additional discussion needed

2.2 Clinical

Section 10.1 provides a brief summary of the clinical development of eluxadoline, including the results from our Phase 3 studies.

3. Does the FDA agree that the conducted clinical development program, including our Phase 1 program, as outlined in Table 10–1 is adequate to support the NDA filing?

FDA Response:

Yes, we agree; however, we recommend that the effects of renal impairment on PK be studied. A reduced PK study may be considered¹.

The potential for drug interactions with gastric acid reducing agents should be addressed in your NDA submission.

Furiex email dated 4/17/14:

Furiex would like to clarify that FDA had previously agreed that a renal study could be conducted post-approval (see Table 6-1 of PreNDA meeting package, correspondence dated 11 June 2012).

Can FDA please confirm our understanding of previous agreements, ie., that the recommendation that we assess the effects of renal impairment on PK can be conducted post-approval?

Additional Discussion:

FDA and Furiex are in agreement. Furiex will conduct a renal impairment study post-approval. Additionally, Furiex confirmed that the ISS will contain a presentation of safety data broken out by mild and moderate renal impairment as determined by Cockcroft-Gault and this was acceptable per the FDA.

¹ Guidance for Industry, Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling <http://www.fda.gov/downloads/Drugs/Guidances/UCM204959.pdf>

FDA denoted at our EOP2 meeting that Furiex needed the following exposures for the NDA: “at least 1000 patients exposed at the to be marketed dose, 300 to 600 patients exposed for at least 6 months, and at least 100 patients exposed at the to be marketed dose for at least one year.”

The following represents the number and duration of exposures to therapeutic doses of eluxadoline from our Phase 2 and Phase 3 studies. Overall there have been 2562 unique human exposures to eluxadoline in our clinical program including Phase 1 normal healthy volunteer and special population studies. Study IBS-3001 is ongoing for long-term safety and therefore we expect another 260 patients (or 430 patients total) will have been exposed to eluxadoline for one-year at time of the 120-day safety update.

Table 9–1 Estimated and Projected Total Eluxadoline Exposures*

	At least 1 BID Dose^a	3 months BID Dosing	6 months BID Dosing	1 year BID Dosing	Est. additional 1 year exposures @ 120-update	Est. total 1 year BID exposures
75 mg BID	807	637	548	91	≈130	≈221
100 mg BID	1032	792	562	79	≈130	≈209
200 mg BID	171	103	---	---	---	---
Total All Strengths^b: 2562						

*As of 24 Jan 2014

^a Includes unique human exposures from Phase 2 and Phase 3 studies only

^b Unique human exposures from all studies including Phase 1

Source: IBS-2001 Table 14.1.2, IBS-3001 Table 14.1.1, IBS-3002 Table 14.1.1, ISS Table 2.15 and 2.29

- Does FDA agree that the extent and duration of exposures listed in Table 9–1 are sufficient to support the filing of the NDA?

FDA Response:

Yes, the extent and duration of exposures appears adequate.

Additional Discussion:

No additional discussion needed

The efficacy and 6-months safety portion of the Phase 3 studies have completed and the results conclude:

- Demonstration of efficacy and safety in ITT patients with data from two similar studies
- Both doses (75 and 100 mg BID) of eluxadoline are effective and demonstrate a dose response
- 75 mg BID is less robust than 100 mg BID

- Eluxadoline is efficacious in both males and females
- Eluxadoline is efficacious at both major time intervals [i.e., at 12-weeks (FDA) and at 26 weeks (EMA)]
- Eluxadoline has a rapid onset of action and retains its effects
- Eluxadoline works by simultaneously reducing BOTH pain and diarrhea
- Eluxadoline is well tolerated
- [REDACTED] (b) (4)

Further detailed efficacy and safety summary information from the Phase 3 studies can be found in Sections 10.1.2 and 10.1.3. As noted earlier, Furiex has chosen to market the 100–mg dose strength of eluxadoline based on its overall safety and efficacy improvement over the 75–mg dose.

5. Based on the safety and efficacy of eluxadoline, does FDA agree with our plans to pursue approval of the 100–mg dose strength only?

FDA Response:

Yes, your plan seems acceptable; however, the final decision on the acceptability of 100 mg over 75 mg dose will be determined during the NDA review.

Additional Discussion:

No additional discussion needed

Safety Narratives/Case Report Forms

Consistent with ICH E3 guidance, Furiex plans to provide safety narratives for all deaths, serious adverse events, and certain other significant adverse events (AEs) as a part of the clinical study reports from our Phase 3 studies in the NDA.

Table 9–2 depicts the other significant adverse events for which narratives will be provided and were based on clinical judgment related to the pharmacological class of eluxadoline (mixed opioid agonist), including known adverse reactions for the drug class, special considerations related to abuse potential, and/or specific requests of FDA (chest pain and cardiovascular events). This same list of other significant adverse events will also be applied program-wide to all studies, except as noted for our human abuse studies (CPS-1006 and CPS-1010). For studies with completed clinical study reports that did not include narratives for these terms, narratives will be created for the NDA and included as appendices to the Integrated Summary of Safety (ISS). Narratives of AEs associated with abuse from Studies CPS-1006 and CPS-1010 to support the 8-factor analysis will accompany the 8-factor in Module 1 of the NDA (see Table 9–3).

Table 9–2 Proposed Strategy for Providing Safety Narratives and/or CRFs in NDA

Type of Adverse Event	Narrative	CRF (or Patient Profile, depending upon study) (includes eluxadoline and placebo)
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Table 9–2 Proposed Strategy for Providing Safety Narratives and/or CRFs in NDA

Type of Adverse Event	Narrative	CRF (or Patient Profile, depending upon study) (includes eluxadoline and placebo)
Death	yes	yes
Serious Adverse Events	yes	yes
Certain Other Significant AEs <ul style="list-style-type: none"> • Some ALT elevations¹ • Chest pain/discomfort • MACE • Euphoric Mood* • Somnolence* • Sedation* • Drunk Feeling* • Angioedema • Non-Serious Pancreatitis • Syncope • Falls • Traffic Accidents 	yes (eluxadoline tx only)	yes
Selected AEs prompting discontinuation <ul style="list-style-type: none"> • Shortness of Breath • Some Abdominal Pain • Diverticulitis • Swollen Throat • Fatigue/ Weakness • Hypothyroidism • Sedation • Dental Implant Loosened • Lipase Increase • Dizziness/Light-headedness • Pruritus/whelps • Worsening Bipolar • Thrombocytopenia • Sphincter of Oddi Spasm • Melena • Depression • Hepatic Steatosis • Prolonged QTc • Seizure • Hypersensitivity 	yes (eluxadoline tx only)	<u>All AEs</u> leading to discontinuation
Dizziness/Lightheadedness AND NOT associated with syncope, traffic accident, fall	no	yes

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; MACE = major adverse cardiac events; tx = treatment

* Does not apply to studies CPS1006 and CPS1010

¹ Pts who are symptomatic, those that lead to discontinuation, and those that meet criteria of >3xULN or >2x baseline ALT

Table 9–3 AE Terms Associated with Abuse (Studies CPS-1006 and CPS-1010)) for Preparation of Safety Narratives and CRFs in NDA

Preferred Term	Verbatim Term(s)
Euphoric Mood	Euphoria, Body Buzz
Somnolence	Drowsiness, Drowsy, Sleepiness, Somnolence, Sleepy
Sedation	Dopiness
Agitation	Excitability
Abnormal Dreams	Vivid Dreams
Feeling of Relaxation	Sense of Relaxation
Feeling Abnormal	Feeling Dazed
Dissociation	Disassociation
Asthenia	Feeling Sluggish
Irritability	Irritable, Irritability

6. Does the Agency agree that these lists are comprehensive and that no additional narratives/CRFs are required for the NDA?

FDA Response:

Yes, the list seems comprehensive, and no additional narratives/CRFs are needed at this time. However, during the course of the review you may be asked to provide additional information if needed. Clarify whether MACE includes the three events-nonfatal MI, nonfatal stroke, and cardiovascular death. Please clarify whether there was any adjudication of your MACE events.

Please provide a rationale for the apparent association between acute hepatobiliary and pancreatitis events seen with your drug in the NDA.

Additional Discussion:

FDA requested that Furiex submit all of the CRFs for the dizziness AEs, not just limited to those events that prompted early discontinuation. Furiex clarified the criteria that they will use for liver injury analysis. The FDA concurred Furiex’s plan to address the association of acute hepatobiliary and pancreatitis event by defining sphincter of Oddi spasm in the NDA submission seem reasonable. Additionally, Furiex also clarified footnote #1 in Table 9-2 regarding ALT elevations. The footnote should have read “for ALT >3X ULN for those with a normal baseline and prescreen OR 2X Baseline if either prescreen or baseline is elevated but it must also meet 3X ULN as well”. FDA requested Furiex include subjects whose AST values increased 3X ULN.

As agreed with the Agency in their written correspondence dated 31 January 2014, rather than a CRF, Furiex plans to supply a “complete patient profile” for patients enrolled in our Phase 2 and Phase 3 studies for certain adverse events (see Table 9–2 above) which coalesces all patient information from 3 electronic sources (eCRF, labs, and patient diaries).

7. A sample patient profile and two sample narratives are provided in this meeting package.
 - a. Is the format of the patient profile sufficient with respect to its “navigate-ability” and content?
 - b. Is the narrative template adequate in supplying the necessary information to review the case?

FDA Response:

Yes, both the formats of the patient profile and the narrative are adequate.

Additional Discussion:

No additional discussion needed

Case Report Tabulations

Furiex plans to provide case report tabulations for all clinical studies, consisting of the datasets, data definition tables and the annotated CRFs (annotated CRFs for Phase 1 studies will not be provided).

8. The SAS data sets exist in ADaM 2.0 under ADaMIG 1.0 and SDTM v1.2, under SDTM-IG 3.1.2. Does the FDA agree these formats are acceptable for the NDA submission?

FDA Response:

Yes, they are acceptable.

Additional Discussion:

No additional discussion needed

9. Does the Agency require the programming code for the statistical analyses performed?

FDA Response:

Yes, you should provide well commented and organized programming code written for each analysis dataset and efficacy table created. Moreover, we recommend programming codes without macros as they are easier to comprehend.

Additional Discussion:

Furiex asked if ASCII format for SAS program is acceptable. FDA will check with Office of Business Informatics (OBI). Furiex clarified that they would not be able to provide the

program without macros because the vendor CRO for programming has the macros patented and is unlikely to release the macros. Furiex further asked if their dataset exceeds the IGB limit for the data submission through the eCTD gateway, whether they should split the dataset or submit the whole dataset outside of the gateway. FDA stated that splitting the dataset seems preferable.

Post Meeting Addendum:

Any submitted programs (scripts) generated by an analysis tool should be provided as ASCII text files or SAS files and should include sufficient documentation to allow a reviewer to understand the submitted programs. If the programs created by the analysis tool use a file extension other than .txt, the file name should include the native file extension generated by the analysis tool for the ASCII text program files, e.g. adsl_r.txt or adsl_sas.txt, etc.

10. As noted earlier, data is entered into an electronic data capture system as well as a patient diary using an interactive voice/web-based system. Neither the patient diary nor the lab data exist in a “case report” format and subsequently exist only as part of the ADaM Define documents, therefore, as annotations will only be supplied for the SDTM define document, there will be no annotation provided for the diary or lab components. Is this acceptable?

FDA Response:

This seems acceptable. However, it is unclear what annotations for the diary or lab components you are referring to. Please confirm that the raw diary and lab data will be provided in the SDTM format. Please also confirm that for all the derived endpoints, the individual data element that was used to calculate the endpoints will be provided with clear documentation of how the endpoints were derived.

Additional Discussion:

Furiex confirmed and FDA agreed that the raw data for the diary and labs will be in SDTM format as well as that for all derived endpoints, and that FDA would receive the individual data element that was used to calculate the endpoints as well as clear documentation of how the endpoints were derived.

11. Our Phase 3 datasets will be based on the same platform used for Phase 2. To familiarize the Agency with these datasets and their format, included in the submission of the meeting package are the Phase 2 datasets including the data definition file. Does the Agency have any feedback regarding the acceptance of these datasets for the NDA submission?

FDA Response:

Your datasets and their format seem acceptable.

Additional Discussion:

No additional discussion needed

2.3 Risk Mitigation Strategy

Section 10.2 describes the benefit/risk assessment of eluxadoline considering data collected from the clinical and nonclinical development program. There is significant unmet medical need in the treatment of moderate to severe IBS-d and eluxadoline provides clinical benefit with manageable risk.

Furiex has identified key risk factors (heavy chronic alcohol use and prior cholecystectomy) associated with the hepatobiliary/pancreatitis adverse events (see Section 10.1.3.1.6). All of these events are mild and reversible and consistent with the etiology of opiate pharmacology. ADME and PK data support the hypothesis that events are local/topical at the sphincter of Oddi, and are not related to direct liver or pancreatic toxicity. Furiex believes that the risks can be easily mitigated in the labeling since:

- These events are infrequent, transient, reversible with lack of sequelae and initial rapid improvement of enzymes, and are associated with identifiable risk factors;
- Patients recognize the symptoms and stop medication;
- There is early onset in the majority of spasm of sphincter of Oddi cases; and
- Similar types of events are described in labeling of other opiates.

Additionally, the NDA will contain our recommendations for

(b) (4)

12. Based on the risk/benefit assessment provided, does the FDA concur that the risks associated with eluxadoline based on its intended use can be addressed with a communication plan including a Medication Guide, as a component of the labeling only and that no formal REMs is required?

FDA Response:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.

Additional Discussion:

No additional discussion needed

2.4 NonClinical

Table 10–48 provides a summary of all nonclinical studies conducted using eluxadoline.

13. Does FDA concur that the nonclinical studies planned for inclusion in the NDA are acceptable/sufficient to support NDA filing?

FDA Response:

Yes, your planned nonclinical studies for inclusion in the NDA appear to be sufficient to support the NDA filing. The acceptability of the studies will be determined during our filing review of the NDA.

Additional Discussion:

No additional discussion needed

14. With respect to the nonclinical data, Furiex plans to provide datasets for the carcinogenicity studies only. These datasets were recently submitted to the IND (IND 79,214/SN 0145) and Furiex plans to resubmit them in the NDA. Are these datasets complete and acceptable for the NDA submission?

FDA Response:

Yes, the dataset for the carcinogenicity studies appear to be complete and are acceptable for the NDA submission.

Additional Discussion:

No additional discussion needed

2.5 Regulatory

15. Are there any other considerations that Furiex should address in our NDA to ensure successful filing?

FDA Response:

See response Question 19. Also, please refer to the “Additional Comments” below.

Additional Discussion:

No additional discussion needed

As a result of receiving Fast Track Designation on 19 January 2011 for the eluxadoline development program, Furiex believes that the NDA would qualify for Priority Review considering the seriousness of IBS-d, specifically its impact on the day-to-day functioning of the

patient, and the potential for eluxadoline to address an unmet medical need. Therefore, Furiex plans to request Priority Review upon the submission of the NDA.

16. Does the FDA agree that this NDA can be assessed under Priority Review?

FDA Response:

We will make that determination at the time of NDA filing.

Additional Discussion:

No additional discussion needed

17. Since eluxadoline is a new molecular entity, does the Agency anticipate needing an Advisory Committee meeting to assess the risks/benefits of eluxadoline in this patient population?

FDA Response:

We will make that determination during the NDA review.

Additional Discussion:

No additional discussion needed

18. There were 779 sites initiated in our Phase 3 trials, however only 71% ever enrolled at least a single patient. Therefore, to comply with the Office of Scientific Investigations' requests for site information at time of the NDA submission, Furiex plans to only supply site information for those sites that ever randomized at least one patient. Does the FDA agree with this approach?

FDA Response:

This approach is acceptable. Please refer to the attached document titled, "OSI Pre-NDA/BLA Request".

Additional Discussion:

No additional discussion needed

As noted earlier, Study IBS-3001 is ongoing for long term safety and last-patient-last-visit is planned for end of July 2014. The NDA submission planned for June 2014 will contain the IBS-3001 clinical study report with the complete efficacy and at least 6-months safety data. Rather than amending the clinical study report during the NDA review cycle, Furiex plans to provide the updated safety data in the 120-day safety update only, focusing only on the additional safety information accrued since the earlier data cut conducted on 24 January 2014.

19. Does the Agency agree with our strategy for the 120-day safety update?

FDA Response:

No, we do not agree. Your NDA should be complete, in its entirety, at the time of submission.

Furiex email dated 4/17/14:

Based on FDA's preliminary response, Furiex believes that there is a misunderstanding. Furiex will be supplying a fully compliant NDA containing complete clinical study reports from both our Phase 3 studies (IBS-3001 and IBS-3002). As we noted in the introductory text to Question 4 and in Table 9-1 of our Pre-NDA meeting package, our initial NDA submission, will contain data from 1110 patients exposed to eluxadoline for 6 months and 170 patients exposed for 1-year.

Recall that Study IBS-3001 is a 52-week double-blind study with a two-week post-treatment follow-up period. As the previously FDA-agreed-upon protocol study design denotes, an extraction of data for statistical analysis was to occur when all patients completed 26 weeks of treatment and at least 100 patients had completed treatment through Week 52. This data extraction forms the basis of the IBS-3001 clinical study report that will be included in the NDA. Our Question 19 above was regarding the format of the 120-day safety update which will include additional long-term safety data for patients in IBS-3001. Specifically, how would FDA like to see these data which we expect to include another 260 patient exposures to eluxadoline for one-year by the 120-day safety update. We had understood from the Agency in previous communications, that the submission of the 120-day safety update does not impact the review clock of a pending application, so we are confused with the above response.

Does the Agency agree with how we plan to provide the 120-day safety update data in light of this clarification?

Additional Discussion:

FDA asked that all IBS-3001 safety data be included in the initial NDA submission. FDA provided different options in order to provide the requested safety data with minimal impact to the timelines: a) delay NDA submission until all patients completed IBS-3001; b) submit rolling NDA with pharmacology/toxicology and CMC sections submitted initially and clinical piece last (date of last piece submitted starts the clock); or c) submit entire NDA as planned in June and then submit the remaining IBS-3001 safety data (in the form of revised ISS) which will trigger a "major amendment" adding three months to the review clock.

Furiex mentioned stopping the controlled safety study early. However, FDA strongly advised Furiex against stopping the controlled safety study early. If a safety issue is identified during the course of the review that could have been resolved by evaluating these additional data, had they existed, a Complete Response could result with a requirement to conduct a long-term safety study pre-approval to resolve the issue.

FDA acknowledged that Furiex is seeking priority review and that the submission of these data in their entirety will help determine the need for an Advisory Committee meeting.

However, FDA indicated that based on the data provided in the meeting package, they had not identified any safety issues of concern at this time.

Post Meeting Addendum:

If you decide to submit the NDA as a Rolling Submission, the following must occur:

- *Request for “rolling review” is to be submitted to the IND and include a schedule for submitting “portions” of the NDA.*
- *Program must continue to meet Fast Track criteria.*
- *Preliminary evaluation of the data supports that the product may be effective.*
- *Cover letter should state “REQUEST FOR SUBMISSION OF PORTIONS OF AN APPLICATION”.*

Also, please review to the guidance titled, “Fast Track Drug Development Programs — Designation, Development, and Application Review”-

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079736.pdf>

FDA acknowledges Furiex’s submission dated April 25, 2014 containing the following question:

Assuming the NDA submission meets all other criteria for filing, if we choose to submit the NDA as originally planned and within 4-months after the initial submission, submit a major amendment with the final integrated safety data as the 120-day safety update (understanding the review clock would be extended another 3 months), would the NDA be considered "acceptable for filing"?

FDA response:

Yes, it will not be considered as a refuse-to-fill issue.

2.6 General

Furiex has some clarifying questions regarding certain Module 1 components. They are as follows:

20. In correspondence dated 06 December 2013, FDA/CSS indicated that the 8-factor analysis should go in Module 1. Can the FDA please clarify what specific section do the scheduling recommendations and the 8-factor analysis go in Module 1?

FDA Response:

CSS has not defined a specific section of Module 1 in which to place 8-factor analysis (8fa). The 8fa is not a requirement but a vehicle for you to provide a proposal for scheduling with

justification. Because module 1 does not contain a specific section for the 8fa, you may place it in section 1.11.4 “Information Not Covered Under Modules 2 to 5.” The 8fa should be easily identifiable. The 8fa should contain links to the data and studies throughout the eCTD used to support the scheduling recommendation.

Additional Discussion:

No additional discussion needed

21. Furiex has yet to identify a marketing/distribution partner for eluxadoline, therefore, has not yet finalized the product trade dress for the labeling. Will FDA accept non-artwork drafts of the immediate and carton labels which exclude final trade-dress for inclusion in the initial NDA submission?

FDA Response:

We would prefer the final drafts of the container labels and carton labeling to be submitted with the initial NDA submission. If that is not feasible, you can submit non-artwork drafts of the container labels and carton labeling with the initial NDA submission. However, you will need to submit the finalized artwork and trade dress within one to two months of your initial NDA submission for our review.

Additional Discussion:

FDA and Furiex are in agreement with submitting the “final draft” labeling with product trade dress within 60 days following the original NDA submission.

22. Furiex received conditional approval of the proprietary name “(b) (4)” on 13 September 2013. In their letter FDA indicated that if any of the product characteristics had changed from the initial submission, the proprietary name should be resubmitted for review. Furiex confirms that no product characteristics have changed. Do we still need to resubmit the original request again to the NDA?

FDA Response:

Yes, as noted in our letter dated September 13, 2013, the proposed name must be submitted for our evaluation with the NDA application.

Additional Discussion:

No additional discussion needed

2.7 Additional Comments:

According to the PK study in subjects with hepatic impairment, the AUC in patient with hepatic impairment can be increased to the level similar to that after intranasal

administration. We recommend that safety profile in patients with hepatic impairment be analyzed by Child/Pugh classification.

We request that in-vitro studies using human materials be submitted in Module 5.

We request that the Question-Based Summary (see attachment titled, “Clinical Pharmacology Summary Aid”) be provided in addition to the Summary of clinical pharmacology.

Additional Discussion:

FDA agreed with Furiex’s plan to submit a meta-analysis of Phase 1 data with high exposure and the AE presentation according to OATP1B1 haplotypes from the (3-month) Phase 2 IBS-d study (See Furiex Slides 3 & 4, Attachment 3). FDA also requested that Furiex assess AEs in patients with high bilirubin.

FDA will check with OBI to see if there is a strict page limit to module 2 to address Furiex’s concern regarding where to place the Question-Based Summary with regards to the size of the document within the NDA submission.

Post Meeting Addendum:

Yes, there is a page limit to module 2. Even though the Question-Based Summary will exceed this limitation, it will process with no issues. The Question-Based Summary should be placed in m.2.3 section, submitted as a single pdf file with proper bookmarks, table of contents, hyperlinks and a clear and concise leaf title so reviewers can quickly identify the document.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Please see above responses, additional discussions, and post meeting addendum where applicable.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion on the need for a REMS was held. Please see above response provided in question 12.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. However, you were provided with three options with submitting your NDA. Please refer to the responses, to include the additional discussion and post meeting addendum, provided in question 19.

4.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge the Agreed initial Pediatric Study Plan dated April 1, 2014.

5.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

6.0 ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

7.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

8.0 ACTION ITEMS

None at this time

9.0 ATTACHMENTS AND HANDOUTS

Furiex's email dated April 17, 2014 and slides dated PowerPoint presentation dated April 21, 2014

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

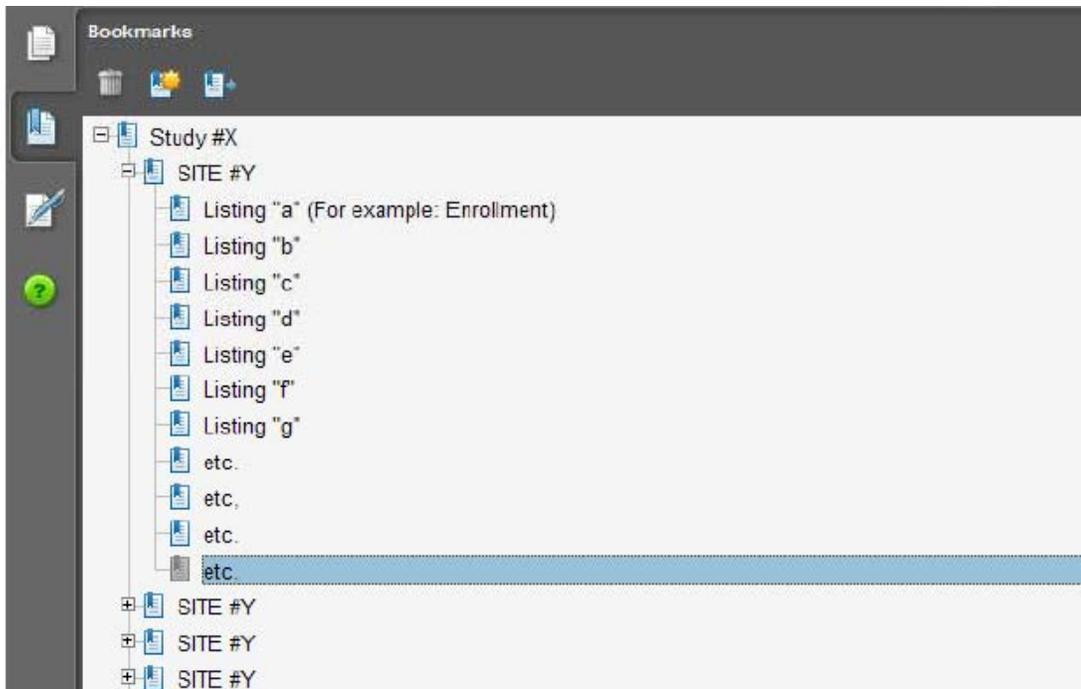
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

- b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

CLINICAL PHARMACOLOGY SUMMARY AID

1. Goal

The goal of this Aid is to facilitate the creation of an optimal Clinical Pharmacology Summary that summarizes the relevant Clinical Pharmacology findings and focuses sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions the Aid provides a generic questionnaire that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

The Clinical Pharmacology Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

2. Question Based Review

2.1 What are the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA?

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies) and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple doses, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug

products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

2.2.3 What are the proposed dosages and routes of administration?

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal $t_{1/2}$ and AUC.

2.4 Exposure-Response

2.4.1 Does the exposure-response relationship support evidence of effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship from randomized and well controlled trials (RCT) and other appropriate studies. Provide evidence that the exposure-response analysis supports evidence of effectiveness: e.g. a significant slope in the E-R relationship or a clear separation in effectiveness at different drug levels and placebo.

Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status see also 2.6/2.7) impacting the exposure-effectiveness relationship. If not identifiable by commonly known covariates, evaluate different strategies, for example therapeutic drug monitoring, to maximize effectiveness for patients with a sub-therapeutic exposure.

Provide point estimate as well as a measure of the inter-subject variability for applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, C_{max} or C_{min} is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

2.4.2 What are the characteristics of the exposure-response relationships for safety?

Describe briefly the method(s) used to determine the exposure-safety relationship. The analysis should focus on adverse events responsible for discontinuations and other drug related toxicities. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex,

race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, C_{max} or C_{min} is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) C_{max} and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

2.4.3 Does this drug prolong QT/QTc Interval?

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Provide information on the criteria used to select the dose regimen (doses, dose intervals) used in the RCTs. Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [C_{max}, t_{max}, AUC, C_{max,ss}, C_{min,ss}, C_{max,ss}/C_{min,ss}, t_{max,ss}, AUC_{0-τ}, CL/F, V/F and t_{1/2} (half-life determining accumulation factor), accumulation factor,

fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, C_{max}, C_{min}, CL/F and t_{1/2} of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?

Indicate absolute and relative bioavailability, lag time, t_{max}, t_{max,ss}, C_{max}, C_{max,ss} and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 What are the characteristics of drug distribution?

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as metabolites in urine and feces.

2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

Provide identification for $\geq 90\%$ of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivity is too small to

be assignable to individual metabolites provide an estimate for their contribution to circulating total radioactivity.

2.5.8 What are the characteristics of drug metabolism?

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance in healthy subjects and patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

2.5.11 What are the characteristics of drug excretion in urine?

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min or mL/min/1.73m²) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

2.5.12 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) C_{max} and AUC values in healthy subjects and patients with the target

disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

2.5.13 How do the PK parameters change with time following chronic dosing?

Indicate whether the mean ratio of AUC_{0-τ} at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C_{max}, C_{min}) in patients with the target disease and how much of the variability is explained by the identified covariates?

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, C_{max}, clearance, volume of distribution and t_{1/2} for pairs studied (e.g. elderly vs. young, male vs. female, normal body weight vs. obese, race/ethnicity(x) vs. race/ethnicity (y), mild vs. severe target disease)

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (change of dose or dose interval or both) is required or not and provide a rationale for either scenario.

2.6.2.1 Severity of Disease State

2.6.2.2 Sex

2.6.2.3 Body Weight

2.6.2.4 Elderly

2.6.2.5 Pediatric Patients

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

2.6.2.6 Race/Ethnicity

2.6.2.7 Renal Impairment

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockcroft-Gault- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, C_{max} and t_{1/2} of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, C_{max} and CL/F on Cl_{cr} for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Indicate mean (SD) for total and renal clearance of the drug in the different sub-groups and provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment (dose or dose interval, or both) is required or not for each of the sub-groups of patients with impaired renal function and provide a rationale for either scenario.

2.6.2.8 Hepatic Impairment

Characterize the demographics for each subgroup (normal hepatic function,

mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC, C_{max}, t_{max} and t_{1/2} of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of C_{max}, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

2.6.2.9 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.7 Extrinsic Factors

2.7.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Summarize the results of the in vitro studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction study in humans is required or is not required

2.7.2 Is the drug a substrate of CYP enzymes?

Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to K_m , controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the *in vitro* findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?

Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for K_i , IC_{50} and V_{max} for each relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ($[I]$). Provide the mean (SD) % activity relative to the positive control for the drug of interest as inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the $[I]/K_i$ ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

2.7.5 Are there other metabolic/transporter pathways that may be important?

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

2.7.7 What are the drug-drug interactions?

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report $t_{1/2}$, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and C_{max} for the drug of interest in the presence and absence of each of the co-administered drugs. Provide a summary statement on the drug interaction liability of the drugs as victim. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Provide a summary statement on the drug interaction liability of the drug as a perpetrator. Report $t_{1/2}$, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and C_{max} for each of the co-administered drugs in the presence and absence of the drug of interest.

2.7.8 Does the label specify co-administration of another drug?

2.7.9 What other co-medications are likely to be administered to the target population?

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

2.8 General Biopharmaceutics

For all *in vivo* studies performed in this section indicate study design,

demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and Cmax after single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

2.8.1 Based on the biopharmaceutical classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

Indicate composition and calories of the food administered, and length of the pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate the clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were the strengths bioequivalent or not?

2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are

the analytical methods used to measure them in plasma and other matrices?

List all assays used and briefly describe the individual methods.

2.9.2 Which metabolites have been selected for analysis and why?

2.9.3 For all moieties measured, is free, bound, or total measured?

Indicate whether free, bound or total (bound+unbound) concentrations of the drug of interest and relevant metabolites are measured and give a rationale for your selection.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Identify all studies that used a particular assay method. For each assay report indicate the corresponding assay validation report.

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

2.9.5.1 What are the lower and upper limits of quantitation?

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

2.9.5.3 What is the sample stability under conditions used in the study?

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at $\leq -20^{\circ}$ C.

2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

2.9.5.5 What evidence is available demonstrating that neither the assay of the drug on interest is impacted by co-administered other drugs and vice versa?

Furiex acknowledges your preliminary responses dated 17 April 2014 and would like to focus our 22 April 2014 PreNDA meeting on responses to Questions 3, 6, 9, 10, 19 and Additional Comments provided regarding Clinical Pharmacology.

In particular we have the following clarifications we would like to make.

Clinical

Section 10.1 provides a brief summary of the clinical development of eluxadoline, including the results from our Phase 3 studies.

Q3: Does the FDA agree that the conducted clinical development program, including our Phase 1 program, as outlined in Table 10–1 is adequate to support the NDA filing?

FDA Response:

Yes, we agree; however, we recommend that the effects of renal impairment on PK be studied. A reduced PK study may be considered.

Furiex Reply:

Furiex would like to clarify that FDA had previously agreed that a renal study could be conducted post-approval (see Table 6-1 of PreNDA meeting package, correspondence dated 11 June 2012).

Can FDA please confirm our understanding of previous agreements, ie., that the recommendation that we assess the effects of renal impairment on PK can be conducted post-approval?

120-Day Safety Update

As noted earlier, Study IBS-3001 is ongoing for long term safety and last-patient-last-visit is planned for end of July 2014. The NDA submission planned for June 2014 will contain the IBS-3001 clinical study report with the complete efficacy and at least 6-months safety data. Rather than amending the clinical study report during the NDA review cycle, Furiex plans to provide the updated safety data in the 120-day safety update only, focusing only on the additional safety information accrued since the earlier data cut conducted on 24 January 2014.

Q19: Does the Agency agree with our strategy for the 120-day safety update?

FDA Response:

No, we do not agree. Your NDA should be complete, in its entirety, at the time of submission.

Furiex Reply:

Based on FDA's preliminary response, Furiex believes that there is a misunderstanding. Furiex will be supplying a fully compliant NDA containing complete clinical study reports from both our Phase 3 studies (IBS-3001 and IBS-3002). As we noted in the introductory text to Question 4 and in Table 9-1 of our Pre-NDA meeting package, our initial NDA submission, will contain data from 1110 patients exposed to eluxadoline for 6 months and 170 patients exposed for 1-year.

Recall that Study IBS-3001 is a 52-week double-blind study with a two-week post-treatment follow-up period. As the previously FDA-agreed-upon protocol study design denotes, an extraction of data for statistical analysis was to occur when all patients completed 26 weeks of treatment and at least 100 patients had completed treatment through Week 52. This data extraction forms the basis of the IBS-3001 clinical study report that will be included in the NDA.

Our Question 19 above was regarding the format of the 120-day safety update which will include additional long-term safety data for patients in IBS-3001. Specifically, how would FDA like to see these data which we expect to include another 260 patient exposures to eluxadoline for one-year by the 120-day safety update. We had understood from the Agency in previous communications, that the submission of the 120-day safety update does not impact the review clock of a pending application, so we are confused with the above response.

Does the Agency agree with how we plan to provide the 120-day safety update data in light of this clarification?

4 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

ANISSA A DAVIS
05/02/2014



IND 79,214

MEETING MINUTES

Furiex Pharmaceuticals, Inc.
Attention: Michelle P. Usher, RAC
Executive Director, Regulatory Affairs
3900 Paramount Parkway, Suite 150
Morrisville, NC 27560

Dear Ms. Usher:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for JNJ-27018966.

We also refer to the meeting between representatives of your firm and the FDA on September 27, 2011. This was an end-of-phase 2 meeting.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1008.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., MBA
Chief, Project Management Staff
Division of Gastroenterology and
Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2 Meeting

Meeting Date and Time: September 27, 2011; 3:00PM
Meeting Location: White Oak Building #22, Conference Room 1417

Application Number: IND 79,214
Product Name: JNJ-27018966
Indication: Diarrhea-Predominant Irritable Bowel Syndrome (IBS-D)
Sponsor/Applicant Name: Furiex Pharmaceuticals, Inc.

Meeting Chair: Ruyi He, M.D.
Meeting Recorder: Brian Strongin, R.Ph., MBA

FDA ATTENDEES

Donna Griebel, M.D. Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Andrew Mulberg, M.D., Deputy Director, DGIEP
Ruyi He, M.D. Medical Team Leader, DGIEP
Lara Dimick M.D. Medical Reviewer, DGIEP
Mike Welch, Ph.D. Team Leader, Biometrics
Sue Chih Lee, Ph.D., Clinical Pharmacology Team Leader
Sushanta Chakder, Ph.D. Supervisory Pharmacologist
Patrick Marroum, Ph.D., Office of New Drug Quality Assurance (ONDQA), Biopharmaceutics Team Leader
Marie Kowblansky, Ph.D., ONDQA, Chemistry, Manufacturing and Controls Team Leader
Michael Klein, Ph.D., Director, Controlled Substance Staff (CSS)
Lori Love, M.D., Ph.D., Lead Medical Officer CSS
Chad Reissig, Ph.D., Pharmacologist, CSS
Brian Strongin, R.Ph., MBA, Chief, Project Management Staff DGIEP

FURIEX ATTENDEES

Paul Covington, M.D. Senior Vice President, Clinical Development & Operations
Gail McIntyre, Ph.D., DABT Senior Vice President, Research
Scott Dove, Ph.D. Executive Director, Clinical Development
Mike Davenport, Ph.D. Executive Director, Clinical Pharmacology & Biostatistics
Michelle Usher, RAC Executive Director, Regulatory Affairs
Tim Costello, Ph.D. Senior Director, Chemistry
Dave Andrae, Ph.D. Director, Biostatistics

JOHNSON & JOHNSON ATTENDEES

Keith Usiskin, M.D. Senior Director, Clinical Development
Umesh Shulka, Ph.D. Senior Director, Compound Development Team Leader

1.0 BACKGROUND

JNJ-27018966 is a mu opioid receptor agonist and a delta opioid receptor antagonist for the treatment of IBS-D. Furiex and the Agency held an end-of-phase 1 meeting March 16, 2010 to discuss the clinical development program and the proposed phase 2 proof-of-concept study. The Agency granted Fast Track designation January 19, 2011. The sponsor has completed a phase 2, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicenter study to evaluate the efficacy, safety, tolerability, and PK, of orally administered JNJ-27018966 in patients with IBS-D. Furiex and the Agency met July 5, 2011 to discuss endpoints for the proposed phase 3 studies based on an interim analysis of the phase 2 study.

The sponsor requested this meeting to discuss their drug development strategy, the acceptability of the proposed phase 3 protocols, and to identify any additional information required to support approval. Furiex plans to conduct two phase 3 safety and efficacy studies to support U.S. approval and a third phase 3 study to support EU approval. They plan to request a separate CMC end-of-phase 2 meeting.

2. DISCUSSION

Nonclinical Questions

NQ-1: Does the Agency agree that the current battery of completed, ongoing and planned nonclinical studies is sufficient for marketing approval?

FDA Response: Your completed, ongoing and planned nonclinical studies appear to be sufficient to support an NDA. Your non-clinical studies indicate abuse potential for your substance. Please see our response to Question RQ-6.

NQ-2: Does the Agency agree to the timing and conduct of the proposed additional nonclinical studies to support marketing approval?

FDA Response: Yes, we agree.

Furiex plans to conduct 2-week i.v. studies (GLP) in rats and primates (see Section 6.3) to support testing of up to 3 single i.v. doses of JNJ-27018966 in crossover fashion in a human abuse potential study.

NQ-3: Does the Agency agree that the planned i.v. toxicology studies will support such a human abuse liability study?

FDA Response: Yes, we agree.

Clinical Questions

Indication Statement and Labeling

In order to make the indication statement more clinically understandable and focused for physicians, Furiex proposes the following indication: “ [REDACTED] (b) (4) [REDACTED] ”

CQ-1: Using the FDA agreed upon composite endpoint of worst abdominal pain in 24 hours and improvement in stool consistency based upon the BSS, does the Agency agree that the Phase 3 studies are adequate to support the proposed label indication of “ [REDACTED] (b) (4) [REDACTED] ”?

FDA Response:

We cannot agree on final wording for the indication until the entire NDA package has been reviewed. This will be part of the labeling discussion at the end of the NDA review.

Adequacy of the Planned Phase 3 Clinical Studies to Support the IBS-d Indication

CQ-2a: Does the Agency agree with how the daily abdominal pain and stool consistency scores are defined and solicited from the study subjects?

FDA Response:

Yes, however to be clear, based on your proposal, to be defined as a responder for each week the subject must have at least 70% of the days of that week recorded (i.e., at least 5 of 7 days). See our response to Question CQ-2b.

CQ-2b: Does the Agency agree with the proposed analysis, multiplicity adjustments and missing data handling methodologies?

FDA Response:

We do not agree. Your primary efficacy endpoint should build upon the definition of a weekly responder. An overall or study responder would then be defined as a subject who is weekly responder for at least 50% of the study weeks. (Also refer to our response to question 2.)

The primary analysis method should be based on the Cochran-Mantel-Haenszel (CMH) test. A logistic regression model based approach can be used as a sensitivity analysis but would be considered exploratory. The proposed Dunnett’s method for multiplicity adjustment is acceptable; however your procedure should maintain control of the study-wise type I error for both primary and key secondary endpoints.

For your primary analysis, we recommend that subjects with fewer than 4 diary days per week be considered missing for the whole week and classified as treatment failures for that week. Your proposed threshold of 5 days per week is also acceptable. For key secondary

analyses, methods should similarly assume subjects with missing data are treatment failures. You should plan several different methods to handle missing data and apply them as sensitivity analyses, including a multiple imputation approach.

Your primary analysis should be based on the ITT population defined by all randomized subjects. All subjects randomized and with at least one post-randomization evaluation would constitute a modified ITT population.

Your Statistical Analysis Plan (SAP) should be finalized and submitted to the Agency for review before the start of study. You should note that all principal components of the analytical plan for primary and secondary endpoint evaluation should be pre-specified at the protocol stage and not introduced in the SAP at a later date.

Discussion:

We agree that it is acceptable to use the daily data analysis for your primary endpoint. However, you should provide weekly analysis for a secondary endpoint.

CQ-2c: Does the Agency agree that the components of the composite endpoint (BSS and categorical 11 point pain scale) are adequate and do not require further content validation in English / Spanish / Other languages?

FDA Response:

Yes, we agree with the current acceptability of composite endpoint that is stated in the draft guidance. However, if you plan to use this in other countries you will need to submit justification to support the validity of the 11 point pain scale and BSS scale in all languages in which you intend to conduct clinical trials.

Discussion:

The Agency will consult SEALD about the Questions in Slide CQ-2C.

Despite not being stated specifically in FDA's version of the Endpoint Guidance meeting minutes dated 02 Aug 2011, Furiex noted in their minutes (Serial Submission 0051) FDA's agreement that (b) (4)

CQ-2d: Can the Agency re-confirm our understanding of the above for purposes of formal documentation of agreement?

FDA Response:

No, we do not agree. To be a composite responder a subject must be a responder in BOTH the abdominal pain and BSS co-primary endpoints.

Discussion;

The assumptions as stated in Furiex's slide CQ-2b are correct.

As noted earlier, Furiex is seeking a global regulatory strategy and regulatory advice on their clinical development program from both the FDA and EU regulators. Our current plan is to power the Phase 3 studies based on the FDA required composite endpoint of pain and BSS. If after discussions with EU and FDA, it is determined that a common study design could support registration in both regions, Furiex would consider conducting only 2 Phase 3 studies incorporating both the FDA (composite of abdominal pain and BSS) and EU (coprimary of abdominal pain and global symptoms) endpoints. In this case, Furiex may consider powering the Phase 3 trials based on the endpoint that is common to both the FDA and EU requirements (ie. abdominal pain) which also drives the largest sample size. This approach increases the overall sample size such that the power with respect to the composite endpoint would be >99%. If acceptable, Furiex would adjust the sample sizes of the proposed protocols and submit the studies with the larger n/arm within our SPA application. Separate Statistical Analysis Plans (SAPs) for submission purposes would be generated for the NDA/MAA.

CQ-2e: Assuming the results are positive and the delta for the composite endpoint is clinically meaningful, would the Agency accept such a strategy?

FDA Response:

Any possible adaptive changes to study designs, endpoints, sample size, or analysis criteria need to be pre-specified prior to start of study in an appropriate planning strategy. Unplanned changes to study endpoints and analysis during the course of the study would likely jeopardize interpretation of the study results.

Discussion:

Furiex's plan as stated in slide CQ-2e may be acceptable if the delta is actually found to be clinically meaningful. It is easiest for the Agency to agree that the difference is clinically meaningful if the difference actually shown is at least the difference targeted in the protocol. A difference lower than that cannot be agreed to be clinically meaningful prior to study conduct.

Justification for the inclusion and exclusion criteria for our Phase 3 studies is provided in Section 10.2.3 of this briefing document. Furiex plans to conduct both Phase 3 studies in patients meeting the Rome III criteria for IBS-d who have clinical manifestations of sufficient intensity at baseline to allow demonstration of a meaningful clinical improvement as well as limit entry into the study of patients at risk for pancreatitis.

CQ-2f: Does the Agency agree with the proposed eligibility criteria?

FDA Response: Yes, we agree

Furiex proposes to dose 100 mg of JNJ-27018966 (b) (4) twice daily based on the results of our POC study. Further justification for our dose selection and regimen are provided in Section 10.2.4.

CQ-2g: Does the Agency agree with our proposed dose and dosing regimen?

FDA Response:

Your proposed dose and dosing regimen i.e. 100 mg BID appears reasonable based on the summary of phase 2 study results. (b) (4)

Appropriateness of IVR Data Collection for Patient-Reported Data

Beginning with the screening period and continuing through the 12-week primary treatment period, IBS symptom data will be collected via an IVRS from the daily diary reports of worst abdominal pain in the past 24 hours, Bristol Stool Scale (BSS) scores, frequency of bowel movements, episodes of bowel incontinence, and episodes of urgency.

After the screening period the IVRS will notify the site whether a patient has met the study entry criteria related to diary compliance, rescue medication use, average of worst abdominal pain in the past 24 hours, and average BSS score. Consistent with the conduct of our Phase 2 study, the actual IVRS data entered by the patients will not be provided to the Investigators at the time of randomization or during the course of the study to prevent any potential bias in subsequent patient entries. IVRS data will be distributed to all sites following database lock and unblinding of the study team.

During the 12-week primary treatment period, notifications from IVRS will be generated to inform Investigators of ongoing patient compliance with diary entries and to alert Investigators if patients have experienced episodes of protocol defined constipation or have required excessive anti-diarrheal rescue medication as defined by the protocol. Investigators will receive automatic notifications from the IVRS as follows:

- Immediately if a patient has 4 consecutive days of no bowel movement as verified by IVRS entries
- Immediately if a patient exceeds the protocol allowable amount of anti-diarrheal rescue medication use as verified by IVRS entries
- Periodically (e.g., once per week) to inform Investigators of patients' compliance in completing the daily diary

In response to an IVRS notification for constipation or excessive rescue medication use, the Investigator must contact the patient within 24 hours to review his/her status. An unscheduled visit to further evaluate the patient's status should be arranged if deemed warranted by the Investigator.

CQ-3a: Does the Agency agree with the process of providing IVRS notifications to the Investigators during the study in lieu of providing raw IVRS data in real time and to prevent bias by not allowing the Investigator access to patient diary entry until after database lock?

FDA Response:

You indicated that as a consequence to the notification, the Investigator may interrupt the study drug at its discretion. Please specify the procedure of interruption and how these patients will be analyzed in the primary analysis.

Discussion:

Furiex will send the Agency a copy of the language in the PRO guidance regarding investigator access to data during the study.

For the purposes of safety reporting, episodes of “constipation” will be captured through traditional adverse event reporting and through continual vigilance of the IVRS. Specifically, 4 consecutive days of no bowel movements as verified by IVRS entries will be classified as constipation and will result in the generation of an automatic notification to the Investigator as described previously. In our Phase 2 study Investigators were required to interrupt the study drug if they received such a notification. The study drug could then be re-started at the Investigator’s discretion if the patient had at least 2 days with a bowel movement and a daily BSS score ≥ 3 within the 4 days immediately after study drug interruption. However, the Investigator was required to permanently discontinue the patient if he or she did not meet the re-start criteria or if the patient experienced more than one episode of 4 consecutive days of no bowel movements. As described in detail in Section 10.1.3.2, only 4 patients (approximately 0.5% of the intent-to-treat population) in our Phase 2 study met the defined centralized criteria for permanent withdrawal for IVRS-confirmed constipation and there were no SAEs involving constipation. Thus, for the planned Phase 3 protocols Furiex will not require mandatory drug interruption based upon centralized monitoring of consecutive absence of bowel movements since no safety signal was observed in Phase 2. In response to an IVRS notification for constipation, the Investigator must contact the patient within 24 hours to review his/her status. Any action to be taken with the study medication will be at the discretion of the Investigator based upon IVRS initiated Investigator notification of diary reports.

CQ-3b: Does the Agency agree with Investigator discretion of study drug management based upon the process of Investigator notification of “constipation” via the IVRS patient diary entry of 4 consecutive days of no bowel movement?

FDA Response:

This approach is acceptable. However, you will need to specify how these patients will be handled in your efficacy analysis.

Discussion:

The Agency agrees with the procedure described in slide CQ-3b.

Clinical Development Plan to Support Marketing Approval

Section 6.4 discusses the JNJ-27018966 clinical development plan while Table 6-2 provides a tabulated summary of completed, ongoing, and planned clinical studies to support marketing approval of JNJ-27018966.

CQ-4a: Does the Agency agree that the completed and planned Phase 1 studies are sufficient for marketing approval?

FDA Response:

Your phase 1 program with completed/proposed studies appears to be acceptable. However, we have following comments for you to further address.

- **We recommend that you conduct a food effect study with the to-be-marketed formulation.**
- **We recommend that you evaluate if your drug is an inhibitor of transporters including but not limited to BSEP. It was noted that the fecal excretion of the radioactivity at 96 hours post-dose is only 68% of the dosed radioactivity. While it is unclear if the radioactivity is from unchanged drug and/or metabolites formed either by human or gut bacteria, the possibility of biliary excretion may not be ruled out at this point.**
- **It was noted that mean C_{max} after multiple doses was about 40% decreased across dose levels (Table 10-1). Since this observation has an implication for potential drug-drug interaction, we request you to address what is the potential mechanism of this observation e.g. inhibition of uptake transporter(s), induction of efflux transporter(s) or induction of metabolizing enzyme(s).**

Reference is made to FDA's meeting minutes from our Endpoint Guidance meeting held on 05 July 2011. In their preliminary responses as well as their final meeting minutes, FDA stated that our safety database would need to contain "greater than 1000 subjects overall, with 300 to 600 subjects exposed for at least 6 months and 100 for one year." As a result of feedback received from this meeting, Furiex has made modifications to the Phase 3 study design affecting the number of total patient exposures. Furiex now estimates that at time of NDA submission, approximately 1600 patients would have been exposed to JNJ-27018966, of which approximately 1000 patients will have up to 12 weeks exposure, at least 300 patients will have been exposed for at least 6 months, and at least 100 patients will have been exposed to one year of treatment.

CQ-4b: Please re-confirm your agreement that the size of the safety premarketing database is adequate for approval?

FDA Response:

The FDA requires at least 1000 patients exposed at the to be marketed dose, 300 to 600 patients exposed for at least 6 months, and at least 100 patients exposed at the to be marketed dose for at least one year. You appear to have met this criteria, however final determination will be made during the NDA review.

Regulatory Questions

Special Protocol Assessment (SPA)

Subsequent to our EOP2 meeting, Furiex plans to request an SPA as per FDA guidance.⁴ Furiex plans to submit a single SPA since the Phase 3 pivotal protocols supporting NDA approval are expected to be identical in design. However, Furiex will be seeking Scientific Advice from regulatory authorities in Europe regarding the Phase 3 study designs as previously mentioned. Should any recommendations received require differences between the two Phase 3 pivotal studies intended for an NDA approval, separate SPAs will be submitted. The SPA(s) will contain the final protocol with relevant questions, the Statistical Analysis Plan (text only, no tables), a sample case report form, and the proposed indication statement.

RQ-1: Is there any other supporting information that should accompany the SPA request that would assist the FDA in their review?

FDA Response:

No.

Pediatric Plan

A brief overview of our pediatric development strategy with supporting rationale can be found in Section 10.3. In accordance with the Pediatric Rule (21 CFR 314.55), Furiex is requesting a waiver for conducting trials in patients aged ^(b)₍₄₎ years and younger. Our rationale for such a waiver is supported by the fact that (1) it is difficult to accurately diagnose IBS-d in this patient population; and (2) the conduct of these studies in this age group is impractical due to endpoints measured for IBS-d.

In addition to the above, Furiex is requesting a deferral for conducting trials in patients aged ^(b)₍₄₎ years and older. Our deferral is based upon completing a full assessment of all of the nonclinical/clinical safety data, the intricacies of study conduct with subjective endpoints in pediatrics, and the probability that the NDA for the adult patient population will be ready for approval prior to the completion of the pediatric studies. Again, further details regarding our rationale for deferral can be found in Section 10.3.

RQ-2a: Considering this disease and the impracticality in conducting the study in the younger pediatric patient population given the endpoints required, does the Agency agree that a request for waiver in patients aged ^(b)₍₄₎ years and younger is appropriate?

FDA Response:

No, see response to RQ-2b below.

RQ-2b: Does the Agency agree that deferring the initiation of pediatric clinical studies (ages (b) (4) to 18) until the submission of JNJ-27018966 NDA for use in the adult population is appropriate and that the approvability of the NDA (for the adult population) is not dependent upon the completion of the pediatric studies?

FDA Response:

The FDA generally will require trials in pediatric patients 6 years, 1 month to 17 years, 12 months, for IBS-D indications, these trials may be deferred until the NDA approval. The pediatric waiver and deferral is requested as part of the NDA submission. The Pediatric Plan submitted by the sponsor to support deferral requests must include a brief description of studies in addition to the protocol submission date, the study completion date and the final report submission date. Final determination will be made by the Pediatric Review Committee during the NDA review.

IBS-d FDA Draft Guidance

In planning our clinical development plan for JNJ-27018966, Furiex extensively studied the FDA draft guidance on IBS clinical development⁵ and engaged in subsequent dialogue with the Agency about upcoming potential revisions to the guidance (see 5 July 2011 Endpoint Guidance meeting minutes). Recognizing that this guidance is draft, and that industry comments have been provided to FDA since its publication, Furiex would like to proactively address any and all further changes planned to the guidance in our development program.

RQ-3a: If changes are being proposed to the guidance, when will the final guidance be available? What are the specific changes?

FDA Response:

The Division cannot guarantee the date of completion.

RQ-3b: Are there any plans to revise the definition of responder with regard to the composite endpoint and, if so, will the new definition align with what Furiex is proposing to use for the Phase 3 program?

FDA Response:

We are considering revisions in the Guidance to the definition of responder for IBS-D. It is unlikely that a revised Guidance will be more conservative than the current draft guidance.

RQ-3c: What are the ramifications to any SPA agreements with the FDA that may be reached prior to the publishing of the final guidance?

FDA Response:

See our response to Question RQ-3b.

See the Guidance for Industry – Special Protocol Assessment at;

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080571.pdf>

“As stated in the PDUFA goals for special protocol assessment and agreement; having agreed to the design, execution, and analyses proposed in protocols reviewed under this process [i.e., carcinogenicity protocols, stability protocols, and phase 3 protocols for clinical trials that will form the primary basis of an efficacy claim], the Agency will not later alter its perspective on the issues of design, execution, or analyses unless public health concerns unrecognized at the time of protocol assessment under this process are evident.”

Discussion:

It is unlikely that the validation of a new PRO instrument after phase 3 studies are initiated would be an issue whether or not an SPA is submitted.

Fast Track and Impact on NDA

As a result of receiving Fast Track Designation on 19 January 2011 for the JNJ-27018966 development program, Furiex believes that the JNJ-27018966 NDA would qualify for *Priority Review* considering the seriousness of IBS-d, specifically its impact on the day-to-day functioning of the patient, and the potential of JNJ-27018966 to address an unmet medical need.

RQ-4a: Can Furiex obtain *Priority Review* for their JNJ-27018966 NDA considering its Fast Track designation?

FDA Response:

This determination will be made within 60 days of the date of the NDA submission.

As allowed with Fast Track programs, Furiex plans to submit a rolling NDA in eCTD format, whereby Furiex would submit Modules of the CTD separately. Based on our preliminary timelines and study completion projections, the carcinogenicity study reports may be the last component to be submitted to the FDA.

RQ-4b: Does the Agency agree that the results from the 2-year carcinogenicity studies can be submitted during FDA’s review of the NDA under a rolling NDA submission?

FDA Response: The carcinogenicity study may be submitted as a rolling submission as part of a complete Module 4.

RQ-4c: Assuming positive response to the above question, and considering our Fast Track designation, can the “PDUFA date” be determined based on the submission of the complete clinical, CMC, and nonclinical sections of the NDA (excluding the carcinogenicity reports)?

FDA Response:

No, the date of the NDA submission is when all of the sections have been submitted to the Agency.

BCS Classification of JNJ-27018966

Although Furiex plans a separate CMC EOP2 meeting with the Agency, Furiex desires to establish BCS classification at this time. Based on the physical properties of JNJ-27018966, the site of action is the GI tract, the choice of commonly used IR formulation excipients proposed for the Phase 3 formulation, human ADME data as well as animal in vivo/in vitro data, the changes from Phase 2 to the Phase 3 formulation have no impact on the Phase 3 clinical program regarding the selection of doses and the safety and efficacy of the new formulation. Supporting data are summarized in Section 10.4.

These data also conclude that JNJ-27018966 is highly soluble, with low permeability and is “rapidly dissolving.” Based on the biopharmaceutics classification system (BCS), Furiex believes that JNJ-27018966 meets BCS III classification. (b) (4)

RQ-5a: Does the Agency agree that JNJ-27018966 is classified as BCS Class III?

FDA Response:

The provided summary information suggests that your drug substance is a BCS Class III. However, we can not agree on the BCS classification of your drug product without a thorough evaluation of the complete information (including raw data).

Please note that the official classification of a BCS Class III drug substance is outside of the scope of the Biopharmaceutics Classification Committee at FDA. Also, note that currently FDA does not grant BA/BE waivers for BCS-Class III drug substances/drug products.

RQ-5b: (b) (4)

FDA Response:

No, we do not agree. Any further change(s) to your formulation needs to be reviewed and the documentation needed to support the change(s) will depend on the specific nature of the change(s).

Abuse Potential

As part of assessing the potential for JNJ-27018966 to be abused, FDA's/CSS's letter dated 8 July 2010 requested Furiex to assess specific physicochemical characteristics of JNJ-27018966 formulation to determine "ease of formulation suitable" to a number of different administration routes (e.g., snorting, chewing, injecting, smoking).

RQ-6: Could FDA/CSS provide more guidance regarding the definitions of "ease" and "suitable?" Are there validated assays for such assessments? Are there references that could be used to guide these assays?

FDA Response:

- **There is not a widely accepted metric or assay to define "ease."**
- **In the context of extracting an active pharmaceutical ingredient (API), "ease" refers to the level of difficulty that a drug abuser would encounter when trying to prepare a solution of the API for intravenous (i.v.) injection, or to obtain a powder that could be used intranasally. The "ease" and extent of extracting the API from intact and manipulated product is determined by *in vitro* studies using a variety of solvents ranging from water to other solvents such as ethanol, rubbing alcohol, ethyl acetate, methylene chloride, bicarbonate solution and others. Effects of temperature, pH, and agitation are also determined. Methods to prepare samples for abuse by snorting, smoking, and i.v. injection should also be explored. This topic has been discussed at Advisory Committee meetings of the Anesthetic & Life Support Drugs Advisory Committee (NDA 22-272, *Oxycontin*, May 5, 2008, and September 24, 2009).**

Additional FDA Comments:

Your protocol does not state what dosage of loperamide will be given as a rescue medication for diarrhea. The protocol should state specific instructions for use of rescue medications for investigators and patients, not just maximum dose.

Your protocol should specifically define the adverse event of constipation. This definition should be based on the BSS and the number of days involved.

We recommend that a pharmacokinetic sample be collected when a serious adverse event occurs in future clinical trials. The time of last dose should be recorded in the case report form.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

[Identify any issues that remain open at the end of the meeting and require further discussion at a later date. If none exist, please indicate that there were no issues requiring further discussion]

5.0 ACTION ITEMS

Action Item/Description	Owner
Consult SEALD about the Questions in Slide CQ-2C.	FDA
[Insert action item with a brief description, if applicable]	Sponsor

6.0 ATTACHMENTS AND HANDOUTS

None

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/s/

BRIAN K STRONGIN
10/26/2011

Executive CAC

Date of Meeting: March 15, 2011

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Al DeFelice, Ph.D., DCRP, Alternate Member
Sushanta K. Chakder, Ph.D., DGP, Supervisory Pharmacologist
Tamal Chakraborti, Ph.D., DGP, Presenting Reviewer

Author of Draft: Tamal Chakraborti, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

The committee did not address the sponsor's proposed statistical evaluation for the carcinogen bioassays, as this does not affect the sponsor's ability to initiate the bioassays. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format-Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008) and the associated Study Data Specifications document.

IND #: 79,214

Drug Name: JNJ-27018966-AAA Oral Tablets

Sponsor: Furiex Pharmaceuticals, Inc. Morrisville, NC

Background: JNJ-27018966 is a locally active, mixed mu-opioid receptor agonist and delta-opioid receptor antagonist that is being developed for the treatment of IBS-d. JNJ-27018966 has low oral bioavailability in all species tested, including humans. JNJ-27018966 acts peripherally, within the gastrointestinal (GI) tract, and has demonstrated efficacy in normalizing GI transit and defecation in animal models of stress-induced or post GI inflammation altered GI function. In the ongoing Phase 2 proof-of-concept study, BID doses of up to 200 mg JNJ27018966 are being evaluated for the treatment of patients with IBS-d. (b) (4)

Mouse Carcinogenicity Study Protocol and Dose Selection

The sponsor proposes to conduct a mouse carcinogenicity study at (b) (4) mg/kg/day. The sponsor's dose selection was based on the results of the 3-month oral toxicity study ((b) (4) Study 1808-006) in CD-1 mice and maximum feasible dose (MFD). Additionally, toxicokinetics (TK), plasma protein binding, metabolism, distribution, excretion and genotoxic profile of JNJ-27018966 information were also provided.

For the 13-week study ((b)(4) Study 1808-006) the no-observed-adverse-effect-level (NOAEL) was 1500 mg/kg/day by oral administration. There were no significant treatment-related effects on mortality, clinical signs, body weight, ophthalmological findings, hematology, clinical chemistry, and urinalysis parameters, or in macroscopic, organ weight, and microscopic examinations in either sex. Increased food consumption for females was seen at 1000 and 1500 mg/kg/day. (b)(4) 1500 mg/kg/day was the highest level achievable with a dose volume of 10 mL/kg and a dose concentration of 150 mg/mL. The sponsor stated that at dose concentrations above 150 mg/mL, formulations could not be loaded and delivered with a syringe and dose needle.

Rat Carcinogenicity Study Protocol and Dose Selection

The sponsor proposes to conduct a 2-year carcinogenicity study in Sprague Dawley (SD) rats with JNJ-27018966 at (b)(4) mg/kg/day. The high dose was selected based on the results of the 3 and 6-month toxicity studies in SD rats (J&J Study TOX8677 and (b)(4) Study 1808-007, respectively) and the MFD.

In the 13-week toxicology study (Study No. TOX8677) at 200 and 1000 mg/kg, PO and 200/5 PO/SC, the NOAELs were 1000 mg/kg/day by oral (PO) administration and 200/5 mg/kg/day by oral and subcutaneous (SC) administration, respectively. Both dose levels were the highest tested dose per route. Based on the findings of the 13-week study, the dose levels for the 26-week rat study ((b)(4) No. 1808-007) were selected as 500, 1000 and 2000 mg/kg/day. (b)(4) , 2000 mg/kg/day was the highest level achievable with a dose volume of 13.3 mL/kg and a dose concentration of 150 mg/mL. No adverse findings were noted in a 13-week interim clinical pathology assessment. There were no significant treatment-related effects on bodyweights, food consumption or clinical observations and there were no mortalities in the 13-week observation period.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee recommended doses of 150, 500, and 1500 mg/kg/day, by oral gavage, based on 1500 being the MFD and setting the mid- and low-dose to clearly separate exposures.

Rat:

- The Committee recommended doses of 150, 500, and 1500 mg/kg/day, based on the MFD. The Committee also recommended that the dose volume should not exceed 10 mL/kg.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DGP
/SChakder, DGP
/TChakraborti, DGP
/RPM/BStrongin/DGP
/ASeifried, OND IO

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/s/

DAVID JACOBSON KRAM
03/16/2011

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 206940

LATE-CYCLE MEETING MINUTES

Furiex Pharmaceuticals, Inc.
Attention: Michelle P. Usher, RAC
Executive Director, Regulatory Affairs
3900 Paramount Parkway Suite 150
Morrisville, North Carolina 27560

Dear Ms. Usher:

Please refer to your New Drug Application (NDA) dated March 11, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for eluxadoline.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on March 4, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jennifer Sarchet, Regulatory Project Manager at 240-402-4275.

Sincerely,

{See appended electronic signature page}

Ruyi He, M.D.
Medical Team Leader
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: March 11, 2015, 9:30 A.M. – 10:30 A.M. ET
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Application Number: 206940
Product Name: Eluxadoline
Applicant Name: Furiex Pharmaceuticals, Inc.

Meeting Chair: Donna Griebel, M.D.
Meeting Recorder: Jennifer Sarchet, RPM

FDA ATTENDEES

Julie Beitz, M.D., Director, Office of Drug Evaluation III
Amy G. Egan, M.D., Deputy Director (Acting), Office of Drug Evaluation III
Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Dragos Roman, M.D., Acting Deputy Director, DGIEP
Joyce Korvick, M.D., M.P.H., Deputy Director for Safety, DGIEP
Laurie Muldowney, M.D., Medical Officer, DGIEP
Sushanta Chakder, Ph.D., Nonclinical Team Leader, DGIEP
Tamal Chakraborti, Ph.D., Nonclinical, DGIEP
Sue-Chih Lee, Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3
Dilara Jappar, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3
Joette Meyer, PharmD., Acting Associate Director for Labeling, DGIEP
Susan Leibenhaut, M.D., Office of Scientific Investigators, Medical Reviewer
Yeh-Fong Chen, Ph.D., Statistical Team Leader, Division of Biometrics III
Jamie Wilkins Parker, MD, OSE/DRISK, Team Leader
Nyedra Booker, M.D., OSE/DRISK, Reviewer
Michael Klein, Ph. D., Director, Controlled Substance Staff Team Leader
Alan Trachtenberg, M.D., Medical Officer, Controlled Substance Staff Reviewer
Silvia N. Calderon, Ph.D., Team Leader Pharmacology, Controlled Substance Staff
Gabiella Anic, Ph.D., Epidemiologist, Division of Epidemiology
Eileen (Ling Yu) Wu, Safety Evaluator Team Leader, Division of Pharmacovigilance
Jennifer Sarchet RN, BSN, MSHA, Regulatory Project Manager, DGIEP

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou, Independent Assessor

APPLICANT ATTENDEES

Paul Covington, M.D.	Senior Vice President, Clinical Development & Operations
Mike Davenport, Ph.D.	Executive Director, Clinical Pharmacology & Biostatistics
Scott Dove, Ph.D.	Executive Director, Clinical Operations
Michelle Usher	Executive Director, Regulatory Affairs

Forest Laboratories, a subsidiary of Actavis plc

Steven Shiff, MD	Executive Director, Clinical Development, Therapeutic Area Head, GI
Darren Weissman, MD	Director, Pharmacovigilance and Risk Management, Global Drug Safety
Kathleen Waldron, MBA	Senior Director, Regulatory Affairs
Ramesh Boinpally, PhD	Fellow, Clinical Pharmacology
Betsy Kurian, PharmD	Fellow, Regulatory Affairs

1.0 BACKGROUND

NDA 206940 was submitted on June 27, 2014 for Eluxadoline

Proposed indication(s): Treatment of adults with irritable bowel syndrome with diarrhea (IBS-D)

PDUFA goal date: May 27, 2015

FDA issued a Background Package in preparation for this meeting on March 4, 2015.

2.0 DISCUSSION

1. Introductory Comments

Discussion: No discussion.

2. Discussion of Minor Review Issues

Controlled Substance Staff (CSS):

CSS met with the applicant on February 25 2015, to discuss the status of the applicant's abuse potential data and assessment, and their Controlled Substances Act (CSA) scheduling proposal. The CSS reviewers noted [REDACTED] (b) (4)

[REDACTED] The CSS reviewers stated that important and relevant information to assess the abuse potential of the drug was not properly evaluated.

After discussion with FDA, the Applicant agreed to re-evaluate all data in the NDA that relate to the abuse potential and dependence liability of the drug. They also agreed to reassess their proposal for scheduling and submit a new proposal for scheduling. The

Applicant was hopeful that they will be able to submit the critical information needed by CSS in a two week time frame following the meeting so that CSS will finalize the review of this NDA and recommend appropriate labeling.

This information that the applicant plans to submit will be used by CSS in developing its recommendation for scheduling under the CSA to the Drug Enforcement Administration (DEA) through the Department of Health and Human Services.

Discussion: Furiex plans to formally submit the above information requests on March 11, 2015. CSS plans to complete the Eight Factor Analysis recommendation by the PDUFA date.

3. Information Requests

Controlled Substance Staff:

- There is a pending submission of a revised proposal for scheduling and an Eight Factor Analysis based on the data in the NDA, which will include data from the GLP toxicology study to address physical dependence.
- There is a pending submission of additional supportive data from the human abuse potential intranasal study.

Discussion: Furiex plans to formally submit the above information requests on March 11, 2015. CSS plans to complete the Eight Factor Analysis recommendation by the PDUFA date.

4. Postmarketing Requirements/Postmarketing Commitments

(1). In –vivo study:

- a. A dedicated renal impairment study. A reduced study design will be acceptable.

Rationale: A dedicated renal impairment study was not conducted in this submission

(2). In-vitro Studies:

- a. In-vitro studies to adequately characterize the metabolism of eluxadoline in respect to various drug metabolizing enzymes. Depending on the results, further studies may be necessary.

Rationale: The in-vitro test systems used to evaluate the potential metabolism (human hepatocytes, microsomes and S9) of eluxadoline were not adequately characterized in respect to various phase 1 and 2 enzymes, prior to the studies. Therefore, metabolism of eluxadoline by phase 1 and 2 enzymes cannot be ruled out.

- b. Further in-vitro studies to predict the in-vivo relevance of time-dependent inhibition of CYP3A4 by eluxadoline. Please refer to current “Guidance for Industry Drug Interaction Studies —Study Design, Data Analysis, Implications for

Dosing, and Labeling Recommendations” for details. Depending on the result, an in-vivo study may be necessary.

Rationale: Preliminary in-vitro data suggest time-dependent inhibition of CYP3A4 by eluxadoline at a concentration (50 μ M) that can be achieved in the gut (Igut is estimated to be 400 μ g/mL or 700 μ M). Further in vitro studies are necessary to allow an adequate assessment of in vivo relevance of this potential interaction.

- c. In-vitro study to estimate the IC50 (or Ki) value of eluxadoline toward P-gp and BCRP and subsequently predict the in-vivo relevance of this interaction. Depending on the result, an in-vivo study may be necessary.

Rationale: Inhibition potential of eluxadoline toward transporters was only evaluated at one concentration, 400 ng/mL (no inhibition was demonstrated), and thus, IC50 (or Ki) values were not determined for this submission. Although the systemic concentration of eluxadoline (Cmax is 2-4 ng/ml) is almost 100-fold lower than the tested concentration, the eluxadoline concentration in the gut (400 μ g/mL) can be about 1000-fold higher than the tested concentration. Therefore, further assessment is necessary.

- d. In-vitro study to evaluate the potential of eluxadoline to inhibit CYP2C8 and induce CYP2B6.

Rationale: Potential of eluxadoline to inhibit CYP2C8 or induce CYP2B6 was not assessed for this submission.

(3). In Vitro Dissolution Study:

The current dissolution specification should remain as an interim analysis for batch release upon approval. Within one year post approval you will need to:

- A. Re-evaluate the dissolution acceptance criterion after dissolution data collected from 30 lots of commercial drug products (15 lots of 75 mg and 15 lots of 100 mg), or a maximum period of 1 year post-launch.
- B. Add a 15- minute time-point to the dissolution test at time of product release and in the stability protocol where profiles will be followed at 10, 15, 20, 30, 45, and 60 minutes.
- C. Assess the dissolution criterion of $Q = \frac{(b)}{(4)}\%$ at 10, 15, or 20-minute time points.
- a. Submit the newly proposed dissolution criterion with supportive dissolution profile data to the Agency for review.

Discussion: Furiex acknowledged and agreed to all Postmarketing Commitments stated above. They will work with the Division to develop the in vitro dissolution data based on unknowns related to when the product can be launched following the scheduling determination.

- (4). Given that eluxadoline is a delta opioid receptor antagonist, a postmarketing, epidemiologic observational safety study to assess for major adverse cardiovascular events (MACE) may be required. Recently approved opioid receptor antagonists have had a post marketing requirement to conduct an observational, epidemiological safety study to assess for MACE.

Discussion: *The applicant noted the low bioavailability of the product and reviewed the retrospective MACE adjudication. There was one event each in the 75 mg and 100 mg drug groups and zero in the placebo group. The FDA noted this is an ongoing discussion.*

5. Major Labeling Issues

As discussed in #3, the in vitro studies to assess the drug interaction potential of eluxadoline were not considered adequate. The potential for eluxadoline to interact with the following classes of drugs will need to be described in labeling, along with instructions for preventing or managing the interaction:

- sensitive CYP3A4 substrates or CYP3A4 substrate drugs with narrow therapeutic index due to potential inhibition of CYP3A4 by eluxadoline.
- sensitive P-gp and BCRP substrates or P-gp and BCRP substrate drugs with narrow therapeutic index due to potential inhibition of P-gp and BCRP in the gut by eluxadoline.
- strong CYP inhibitors as the metabolic pathway of eluxadoline is unclear.

Discussion: *The applicant agreed they will do safety analysis of each of the above subgroups and submit this data as soon as possible.*

Additional Discussion: *The applicant will provide a revised section 5 language related to Sphincter of Oddi Dysfunction (SOD).*

6. Review Plans

After the applicant resubmits to the NDA a new revised scheduling proposal and an adequate assessment of abuse potential of eluxadoline, CSS will prepare a review considering the new material, make recommendations for labeling of Section 9.0 and other relevant sections of the labeling and prepare a recommendation for scheduling in the CSA for transmittal to the DEA.

Discussion: *The FDA clarified that no discipline review letters are planned.*

7. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

RUYI HE
04/10/2015



NDA 206940

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Furiex Pharmaceuticals, Inc.
Attention: Michelle P. Usher, RAC
Executive Director, Regulatory Affairs
3900 Paramount Parkway Suite 150
Morrisville, North Carolina 27560

Dear Ms. Usher:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for eluxadoline.

We also refer to the Late-Cycle Meeting (LCM) scheduled for March 11, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Jennifer Sarchet, Regulatory Project Manager, at 240-402-4275.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: March 11, 2015 9:30 A.M. – 10:30 A.M. ET
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Application Number: 206940
Product Name: Eluxadoline
Indication: Treatment of irritable bowel syndrome with diarrhea in adults
Sponsor/Applicant Name: Furiex Pharmaceuticals, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

There are no substantive review issues at this time.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Minor Review Issues – 10 minutes

Controlled Substance Staff (CSS):

CSS met with the applicant on February 25 2015, to discuss the status of the applicant's abuse potential data and assessment, and their Controlled Substances Act (CSA) scheduling proposal. The CSS reviewers noted (b) (4)

[REDACTED] The CSS reviewers stated that important and relevant information to assess the abuse potential of the drug was not properly evaluated.

After discussion with FDA, the Applicant agreed to re-evaluate all data in the NDA that relate to the abuse potential and dependence liability of the drug. They also agreed to reassess their proposal for scheduling and submit a new proposal for scheduling. The Applicant was hopeful that they will be able to submit the critical information needed by CSS in a two week time frame following the meeting so that CSS will finalize the review of this NDA and recommend appropriate labeling.

This information that the applicant plans to submit will be used by CSS in developing its recommendation for scheduling under the CSA to the Drug Enforcement Administration (DEA) through the Department of Health and Human Services.

3. Information Requests – 5 minutes

Controlled Substance Staff:

- There is a pending submission of a revised proposal for scheduling and an Eight Factor Analysis based on the data in the NDA, which will include data from the GLP toxicology study to address physical dependence.
- There is a pending submission of additional supportive data from the human abuse potential intranasal study.

4. Postmarketing Requirements/Postmarketing Commitments – 15 minutes

(1). In –vivo study:

- a. A dedicated renal impairment study. A reduced study design will be acceptable.

Rationale: A dedicated renal impairment study was not conducted in this submission

(2). In-vitro Studies:

- a. In-vitro studies to adequately characterize the metabolism of eluxadoline in respect to various drug metabolizing enzymes. Depending on the results, further studies may be necessary.

Rationale: The in-vitro test systems used to evaluate the potential metabolism (human hepatocytes, microsomes and S9) of eluxadoline were not adequately characterized in respect to various phase 1 and 2 enzymes, prior to the studies. Therefore, metabolism of eluxadoline by phase 1 and 2 enzymes cannot be ruled out.

- b. Further in-vitro studies to predict the in-vivo relevance of time-dependent inhibition of CYP3A4 by eluxadoline. Please refer to current “Guidance for Industry Drug Interaction Studies —Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations” for details. Depending on the result, an in-vivo study may be necessary.

Rationale: Preliminary in-vitro data suggest time-dependent inhibition of CYP3A4 by eluxadoline at a concentration (50 uM) that can be achieved in the gut (I_{gut} is estimated to be 400 ug/mL or 700 uM). Further in vitro studies are necessary to allow an adequate assessment of in vivo relevance of this potential interaction.

- c. In-vitro study to estimate the IC₅₀ (or K_i) value of eluxadoline toward P-gp and BCRP and subsequently predict the in-vivo relevance of this interaction. Depending on the result, an in-vivo study may be necessary.

Rationale: Inhibition potential of eluxadoline toward transporters was only evaluated at one concentration, 400 ng/mL (no inhibition was demonstrated), and thus, IC₅₀ (or K_i) values were not determined for this submission. Although the systemic concentration of eluxadoline (C_{max} is 2-4 ng/ml) is almost 100-fold lower than the tested concentration, the eluxadoline concentration in the gut (400 ug/mL) can be about 1000-fold higher than the tested concentration. Therefore, further assessment is necessary.

- d. In-vitro study to evaluate the potential of eluxadoline to inhibit CYP2C8 and induce CYP2B6.

Rationale: Potential of eluxadoline to inhibit CYP2C8 or induce CYP2B6 was not assessed for this submission.

(3). In Vitro Dissolution Study:

The current dissolution specification should remain as an interim analysis for batch release upon approval. Within one year post approval you will need to:

- A. Re-evaluate the dissolution acceptance criterion after dissolution data collected from 30 lots of commercial drug products (15 lots of 75 mg and 15 lots of 100 mg), or a maximum period of 1 year post-launch.
- B. Add a 15- minute time-point to the dissolution test at time of product release and in the stability protocol where profiles will be followed at 10, 15, 20, 30, 45, and 60 minutes.
- C. Assess the dissolution criterion of $Q = \frac{(b)}{(4)}\%$ at 10, 15, or 20-minute time points.
 - a. Submit the newly proposed dissolution criterion with supportive dissolution profile data to the Agency for review.

(4). Given that eluxadoline is a delta opioid receptor antagonist, a postmarketing, epidemiologic observational safety study to assess for major adverse cardiovascular events (MACE) may be required. Recently approved opioid receptor antagonists have had a post marketing requirement to conduct an observational, epidemiological safety study to assess for MACE.

5. Major labeling issues – 10 minutes

As discussed in #3, the in vitro studies to assess the drug interaction potential of eluxadoline were not considered adequate. The potential for eluxadoline to interact with the following classes of drugs will need to be described in labeling, along with instructions for preventing or managing the interaction:

- sensitive CYP3A4 substrates or CYP3A4 substrate drugs with narrow therapeutic index due to potential inhibition of CYP3A4 by eluxadoline.
- sensitive P-gp and BCRP substrates or P-gp and BCRP substrate drugs with narrow therapeutic index due to potential inhibition of P-gp and BCRP in the gut by eluxadoline.
- strong CYP inhibitors as the metabolic pathway of eluxadoline is unclear.

6. Review Plans – 10 minutes

After the applicant resubmits to the NDA a new revised scheduling proposal and an adequate assessment of abuse potential of eluxadoline, CSS will prepare a review considering the new material, make recommendations for labeling of Section 9.0 and other relevant sections of the labeling and prepare a recommendation for scheduling in the CSA for transmittal to the DEA.

7. Wrap-up and Action Items – 5 minutes

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

/s/

DONNA J GRIEBEL
03/04/2015