CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207963Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 207963 SUPPL # HFD # 180

Trade Name Palonosetron Hydrochloride Injection

Generic Name

Applicant Name Exela Pharma Sciences, LLC.

Approval Date, If Known Approval issued on 8/22/16

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

b) 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 ☐

Note: The clinical investigation reviewed (Study EPS-2014-001) is a clinical safety study and not a clinical effectiveness study. There were no studies submitted for efficacy. The applicant is relying on FDA's finding of efficacy for ALOXI.

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.

Not applicable (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

c) Did the applicant request exclusivity?

YES ☐ NO ☒

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

d) 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?

NO

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#	021372	Aloxi (palonosetron hydrochloride) injection
NDA#	022233	Aloxi (palonosetron hydrochloride) capsule
NDA#	205718	Akynzeo (netupitant and palonosetron) capsule
NDA#	203050	Palonosetron Hydrochloride Injection

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 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 ☐

Note: The clinical investigation reviewed (Study EPS-2014-001) is a clinical safety study and not a clinical effectiveness study. It is not a clinical investigation that demonstrates effectiveness. There were no studies submitted for efficacy. The applicant is relying on FDA's finding of efficacy for ALOXI.

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 ☐

Note: The clinical investigation reviewed (Study EPS-2014-001) is a clinical safety study and not a clinical effectiveness study. It is not a clinical investigation that demonstrates effectiveness.

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:

EPS-2014-001

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 ☒

Note: The clinical investigation reviewed (Study EPS-2014-001) is a clinical safety study and not a clinical effectiveness study. It is not a clinical investigation that demonstrates effectiveness.

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 ☒

Note: The clinical investigation reviewed (Study EPS-2014-001) is a clinical safety study and not a clinical effectiveness study. It is not a clinical investigation that demonstrates effectiveness.

Investigation #2 YES ☐ NO ☐

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

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

EPS-2014-001

Note: The clinical investigation reviewed (Study EPS-2014-001) is a clinical safety study and not a clinical effectiveness study. It is not a clinical investigation that demonstrates effectiveness.

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

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

Investigation #1		!
		!
IND # 116583	YES ☒	! NO ☐
		! Explain:

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

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

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

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: Mary Chung, PharmD.
Title: Regulatory Project Manager
Date: 8/22/16

Name of Office/Division Director signing form: Joyce Korvick, M.D., M.P.H.
Title: Deputy Director for Safety, Division of Gastroenterology and Inborn Errors Products

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

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/s/

MARY H CHUNG
08/22/2016

JOYCE A KORVICK
08/22/2016

From:	Chung, Mary
To:	jsterling@exela.us
Cc:	Chung, Mary
Subject:	NDA 207963 palonosetron - FDA Proposed PI PPI
Date:	Friday, March 18, 2016 12:36:27 PM
Attachments:	NDA 207963 palonosetron FDA proposed PI 3-18-16.docx NDA 207963 palonosetron FDA proposed PI 3-18-16.pdf NDA 207963 palonosetron FDA proposed PPI 3-18-16.docx NDA 207963 palonosetron FDA proposed PPI 3-18-16.pdf

Jonathan,
Reference is made to your resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for palonosetron hydrochloride injection, 0.125 mg/mL received September 22, 2015.

On March 14, 2016, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure (PI, PPI). We request that you resubmit labeling (PI, PPI) that addresses these issues to the NDA by March 21, 2016.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting 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 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

We request that you resubmit labeling (PI, PPI) that addresses these issues to the NDA by Monday March 21, 2016.
We also request you provide an the e-copy of the PI and PPI to be submitted to the NDA by March 21, 2016, via email on March 21, 2016.

Please confirm receipt of this correspondence.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MARY H CHUNG
03/18/2016

Chung, Mary

From: Chung, Mary
Sent: Thursday, March 10, 2016 2:04 PM
To: jsterling@exela.us
Cc: Chung, Mary
Subject: FW: NDA 207963 palonosetron - FDA Proposed PI PPI

Jonathan,
Reference is made to your resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for palonosetron hydrochloride injection, 0.125 mg/mL received September 22, 2015.

Additional reference is made to our March 9, 2016 correspondence, which contained our proposed revisions to the PI, PPI in response to your labeling submission dated March 3, 2016.

Reference is made to the below section under section 14 of the PI. When resubmitting labeling (PI, PPI) that addresses our March 9, 2016 labeling comments/edits to the NDA, please also include the below revisions.

> 14 CLINICAL STUDIES
> The safety and efficacy of Palonosetron HCl Injection have been established based on adequate and well-controlled adult studies of another intravenous formulation of palonosetron HCl in chemotherapy induced nausea and vomiting (b) (4). Below is a display of the results of these adequate and well-controlled studies of palonosetron HCl (b) (4)

We request that you resubmit labeling (PI, PPI) that addresses our March 9, 2016 labeling comments/edits, and the above, to the NDA by Monday March 14, 2016.

Please confirm receipt of this correspondence.

Regards,
Mary

From: Chung, Mary
Sent: Wednesday, March 09, 2016 2:32 PM
To: jsterling@exela.us
Cc: Chung, Mary
Subject: NDA 207963 palonosetron - FDA Proposed PI PPI

Jonathan,
Reference is made to your resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for palonosetron hydrochloride injection, 0.125 mg/mL received September 22, 2015.

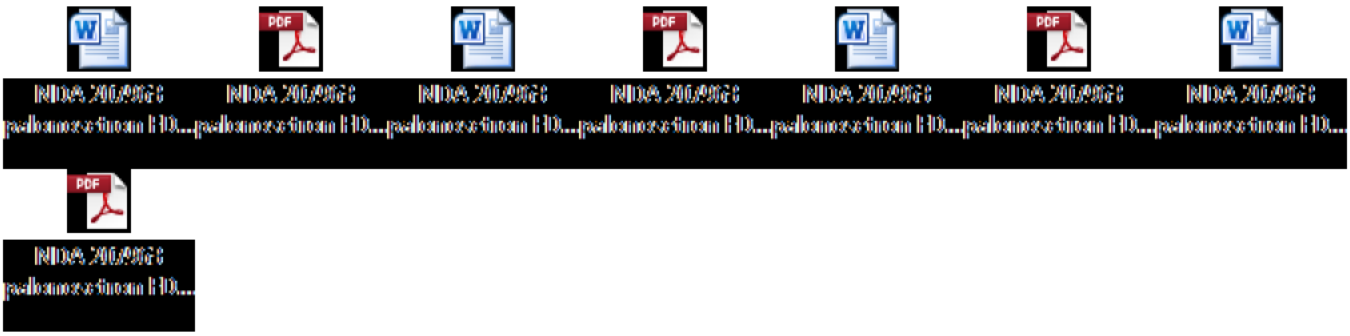
On March 3, 2016, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure (PI, PPI). We request that you resubmit labeling (PI, PPI) that addresses these issues to the NDA by Monday March 14, 2016.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting 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 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Could you please confirm receipt of this correspondence?



Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
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mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
03/10/2016

From:	Chung, Mary
To:	jsterling@exela.us
Cc:	Chung, Mary
Subject:	NDA 207963 palonosetron - FDA Proposed PI PPI
Date:	Wednesday, March 09, 2016 2:32:00 PM
Attachments:	NDA 207963 palonosetron FDA Proposed PI clean copy 3-9-16.docx NDA 207963 palonosetron FDA Proposed PI clean copy 3-9-16.pdf NDA 207963 palonosetron FDA Proposed PI tracked changes 3-9-16.docx NDA 207963 palonosetron FDA Proposed PI tracked changes 3-9-16.pdf NDA 207963 palonosetron FDA Proposed PPI clean copy 3-9-16.docx NDA 207963 palonosetron FDA Proposed PPI clean copy 3-9-16.pdf NDA 207963 palonosetron FDA Proposed PPI tracked changes 3-9-16.docx NDA 207963 palonosetron FDA Proposed PPI tracked changes 3-9-16.pdf

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Jonathan,
Reference is made to your resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for palonosetron hydrochloride injection, 0.125 mg/mL received September 22, 2015.

On March 3, 2016, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure (PI, PPI). We request that you resubmit labeling (PI, PPI) that addresses these issues to the NDA by Monday March 14, 2016.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting 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 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Could you please confirm receipt of this correspondence?

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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/s/

MARY H CHUNG
03/09/2016

From: Chung, Mary
To: jsterling@exela.us
Cc: Chung, Mary
Subject: NDA 207963 palonosetron- Carton Container Label
Date: Friday, March 04, 2016 12:35:27 PM

Jonathan,
Reference is made to your resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for palonosetron hydrochloride injection, 0.125 mg/mL received September 22, 2015.

On February 5, 2016, we received your proposed carton container label submission to this application, and have the following comments. We request that you submit carton container labeling that addresses these issues to the NDA by March 9, 2016, or before.

1. We recommend bolding the cautionary statement, (b) (4) located on the Principal Display Panel, to ensure that this important information is not overlooked by health care providers.
2. Relocate the "Rx only" statement, currently on the side panel, to the Principal Display Panel.

Please confirm receipt of this correspondence.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
03/04/2016

From:	Chung, Mary
To:	jsterling@exela.us
Cc:	Chung, Mary
Subject:	NDA 207963 palonosetron- FDA Proposed PI and PPI
Date:	Thursday, February 25, 2016 5:43:18 PM
Attachments:	NDA 207963 palonosetron FDA Proposed PI 2-25-16 Tracked Changes.docx NDA 207963 palonosetron FDA Proposed PI 2-25-16 Tracked Changes.pdf NDA 207963 palonosetron FDA Proposed PI 2-25-16 clean copy.docx NDA 207963 palonosetron FDA Proposed PI 2-25-16 clean copy.pdf NDA 207963 palonosetron FDA Proposed PPI 2-25-16.docx NDA 207963 palonosetron FDA Proposed PPI 2-25-16.pdf

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Jonathan,
Reference is made to your resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for palonosetron hydrochloride injection, 0.125 mg/mL received September 22, 2015.

On September 22, 2015, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure (PI, PPI). We request that you resubmit labeling (PI, PPI) that addresses these issues by Tuesday March 1, 2016.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting 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 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please confirm receipt of this correspondence.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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/s/

MARY H CHUNG
02/25/2016

From:	Chung, Mary
To:	jsterling@exela.us
Cc:	Chung, Mary
Subject:	NDA 207963 palonosetron I.V. - Carton/Container Label
Date:	Monday, February 01, 2016 2:37:19 PM
Attachments:	2-1-16 NDA 207963 carton container FDA Comments.pdf

Jonathan,
Reference is made to your resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for palonosetron hydrochloride injection, 0.125 mg/mL received September 22, 2015.

On August 7, 2014, we received your proposed carton/container label submission to this application, and have the attached comments and recommendations.

We request that you resubmit carton/container labeling that addresses these issues by February 8, 2016, to the NDA.
Please confirm receipt of this correspondence.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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Phone: 301-796-0260 /fax: 301-796-9904
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FDA Comments/ Recommendations on NDA 207963 palonosetron I.V. Carton/Container Labels

1. Add a cautionary statement in red to the principal display panel that this product is higher in concentration than the reference listed drug product to avoid dosing errors. For example, [redacted]

2. To mitigate the risk of confusion with the reference listed drug's strength and subsequent dosing errors, we recommend revising the statement of strength to total quantity per total volume, followed by the concentration per milliliter (mL) in a different color than the established name. Revise the statement of strength to the following:

   0.25 mg/2 mL
   (0.125 mg/mL)

3. Increase the prominence of the established name by increasing the font size.

4. As currently presented, the NDC number is located at the bottom of the carton labeling. Since NDC number is often used as an additional verification prior to drug dispensing in the pharmacy, it is an important safety feature that should be prominently displayed in the top third of principal display panel of the labeling, in accordance with 21 CFR 207.35(3)(i). Relocate the NDC number from the side panel to the top third of the principal display panel.

5. As currently presented, there are [redacted] Rx only statements on the side panel. Please move one statement to the bottom right corner of the principal display panel [redacted]

6. Add a usual dosage statement to the side panel. For example, "Usual dose: See prescribing information".

7. Remove the trailing zero from the strength presentation (0.25 mg/2 mL) to avoid misinterpretation of the product strength.

8. Delete the "[redacted]" statement since the proposed adult dosage for this formulation is the entire vial (0.25 mg).

9. Revise the "[redacted] statement to "2 mL single dose sterile vial" since the term "single dose" accurately describes the correct usage of this product in single patient as a single injection[1].

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf

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/s/

MARY H CHUNG
02/01/2016

Chung, Mary

From: Chung, Mary
Sent: Thursday, December 17, 2015 3:02 PM
To: 'Jonathan Sterling'
Cc: Chung, Mary
Subject: NDA 207963 palonosetron I.V.- Information Request

Jonathan,
Reference is made to your resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for palonosetron hydrochloride injection, 0.125 mg/mL received September 22, 2015.

> It appears that Helsinn and Roche received notice under 21 CFR 314.52 for newly listed patents '980 and '905. With respect to any other owner(s) of these newly listed patent(s) that are the subject of the certification or the representative designated by the owner to receive notice, please submit to FDA adequate documentation of receipt of notice, or re-notify the relevant recipients and submit to FDA adequate documentation of receipt of notice for patents '980 and '905. You did not submit a return receipt or letter acknowledging receipt by the person(s) provided notice. See 21 CFR 314.52. We note that FDA did not agree to another form of documentation in advance.
>
> Additionally, for patent '942, with respect to any owner(s) of this newly listed patent(s) that are the subject of the certification or the representative designated by the owner to receive notice, please submit to FDA adequate documentation of receipt of notice.

We request your response be received to the NDA by January 5, 2016, or before.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
12/17/2015

Chung, Mary

From: Chung, Mary
Sent: Thursday, October 29, 2015 12:56 PM
To: jsterling@exela.us
Cc: Chung, Mary
Subject: NDA 207963 palonosetron I.V.- Nonclinical Information Request

Jonathan,
Reference is made to your resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for palonosetron hydrochloride injection, 0.125 mg/mL received September 22, 2015.

We have the following request for additional information:

> According to the study report for "Human Blood Hemolysis Screening of a Test Agent" (Study No. CYP1177-R4), two-fold dilutions of each test article were prepared in saline and then diluted into aliquots of blood. Please confirm whether the test article was first diluted with saline (prior to dilution in blood) at all test concentrations evaluated in this study (test concentration range of 0.098 mcg/ml to 12.5 mcg/ml).

We request to receive your response to the NDA by November 2, 2015, or before.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
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mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
10/29/2015

Chung, Mary

From: Chung, Mary
Sent: Friday, October 23, 2015 1:54 PM
To: jsterling@exela.us
Cc: Chung, Mary
Subject: NDA 207963 palonosetron

Jonathan,
Reference is made to your resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for palonosetron hydrochloride injection, 0.125 mg/mL received September 22, 2015.

Additional reference is made to your amendment received October 7, 2015 containing patent information for patent 9125905.

Please submit to the NDA, the documentation of notice (certified mail return receipts) of the patent certification for patent 9125905.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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/s/

MARY H CHUNG
12/02/2015

From: Carr, James
To: "Jonathan Sterling"
Subject: NDA 207963 Palonosetron-Exela Information Request
Date: Monday, June 01, 2015 4:06:00 PM
Attachments: image001.png

Mr.s Sterling,

Below are Information Requests that we will discuss tomorrow afternoon.

1. On March 25, 2015, you notified FDA that legal action was taken by Helsinn Healthcare S.A. and Roche Palo Alto LLC related to patent numbers 8,518,218 and 8,518,981 and that this legal action was taken within 45 days of receipt of the notice of certification. Confirm for patent numbers 7,947,724, 7,947,725, 7,960,424, 8,598,219, and 8,729,094 for which Exela Pharma provided FDA with Paragraph IV Certification, that legal action by the patent owner or their representatives or application holder was not taken within 45 days of receipt of the notice of certification.
2. On March 24, 2015, you provided FDA with a "certification of patent holder notification and a copy of the USPS return receipts" that were intended to serve as documentation of receipt of notice as required under 21 CFR 314.52(e). Based on the March 24, 2015, submission, it is not explicitly clear that the documentation provided demonstrates each person that was provided the notice as required under 21 CFR 314.52(a). Provide a written description clarifying how the documentation provided demonstrates that each patent owner or their representatives and the NDA holder received the required notice. Provide additional evidence, as necessary, to further support your written description.
3. On May 13, 2015, you provided FDA with an updated certification of patent notification with specific reference to the notice content requirements of 21 CFR 314.52(c), however, several references are made to 21 CFR 314.95 (i.e., requirements applicable to ANDA's, rather than a 505(b)(2) application). Update your certification statement so that it provides the appropriate references to 21 CFR 314.52.

Jay

James B Carr, MPAS, PA-C
LCDR, US Public Health Service
Regulatory Health Project Manager
CDER/OND/ODEIII
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

(240) 402-6624 (office)
(301) 796-9904 (fax)
James.Carr@fda.hhs.gov

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/s/

JAMES B CARR
06/02/2015

From:	Keyvan, Laya
To:	jsterling@exela.us
Cc:	Carr, James
Subject:	Information Request for NDA 207963
Date:	Tuesday, April 21, 2015 10:47:00 AM
Attachments:	image001.png
Importance:	High

Dear. Mr. Sterling,

We are referring to your NDA 207963. The following Information Request is needed to continue reviewing your application by COB April 27, 2015:

1. Submit a revised statement of composition for Palonosetron Injection which includes the changes made in the amendment dated December 31, 2014.
2. Submit a revised batch composition statement to your NDA which incorporates the changes made in the amendment dated December 31, 2014 (b) (4) .
3. Submit a revised list of process controls for the manufacturing process used to produce Palonosetron Injection, which incorporates the changes made in the amendment dated December 31, 2014 (b) (4)

Please let me know if you have any questions/concerns. Also, please confirm the receipt of this email.

Thanks,

Laya Keyvan, MS, MBA
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-4598
Email: laya.keyvan@fda.hhs.gov

Laya Keyvan -A

Digitally signed by Laya Keyvan -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Laya Keyvan -A, 0.9.2342.19200300.100.1.1=2001367756
Date: 2015.04.21 10:48:24 -04'00'

OFFICE OF PHARMACEUTICAL QUALITY

From:	Carr, James
To:	"Jonathan Sterling"
Cc:	LCDR R. Wes Ishihara; CDR Matt Brancazio
Subject:	NDA 207963 Palonosetron Information Request
Date:	Tuesday, March 17, 2015 4:04:00 PM
Attachments:	image001.png

Mr. Sterling,

Under 21 CFR 314.54(a)(1)(vi), a 505(b)(2) application must contain a patent certification or statement with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on for approval of the application were conducted, or that claim a use for the listed or other drug. Your 505(b)(2) application relies upon the Agency's finding of safety and effectiveness for NDA 021372 for ALOXI® (Palonosetron hydrochloride) injection dosage form, for which you submitted Paragraph IV certification with respect to U.S. Patent Numbers:

Patent NO. 7,947,724
Patent NO. 7,947,725
Patent NO. 7,960,424
Patent NO. 8,518,981
Patent NO. 8,598,218
Patent NO. 8,598,219
Patent NO. 8,729,094

The above patents are listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) as described in 21 CFR 314.54(a)(1)(vi)). However, you have not provided documentation of receipt by each person identified in 21 CFR 314.52(a) of the required notice of Paragraph IV certification for the ALOXI patents listed above. Acceptable forms of documentation are described in 21 CFR 314.52(e).

Additionally, you stated in a teleconference with FDA on March 4, 2015, that a lawsuit was filed by the patent owner against Exela; however, upon removal of the pH adjusters, you also stated that the lawsuit has been dropped. Please provide documentation supporting this statement.

Jay

James B Carr, MPAS, PA-C
LCDR, US Public Health Service
Regulatory Health Project Manager
CDER/OND/ODEIII
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

(240) 402-6624 (office)
(301) 796-9904 (fax)
James.Carr@fda.hhs.gov

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/s/

JAMES B CARR
03/26/2015

From:	Carr, James
To:	"Jonathan Sterling"
Cc:	LCDR R. Wes Ishihara
Subject:	NDA 207963 Palonosetron CMC Telephone Conference questions for discussion 2-4-2015
Date:	Wednesday, February 04, 2015 11:46:00 AM
Attachments:	image001.png

Mr. Sterling,
Good morning the following are questions that the CMC team want to focus on:

1. Please provide justification for your amendment in terms of its effect on the safety and/or efficacy of the product.
2. So that we may further evaluate your proposed change please tabulate the following information for the four registration batches and the clinical batch used in the local irritation study
   a-Batch size

(b) (4)

Jay
James B Carr, MPAS, PA-C
LCDR, US Public Health Service
Regulatory Health Project Manager
CDER/OND/ODEIII
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

(240) 402-6624 (office)
(301) 796-9904 (fax)
James.Carr@fda.hhs.gov

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/s/

JAMES B CARR
03/03/2015

From:	Keyvan, Laya
To:	jsterling@exela.us
Subject:	Information Request for NDA 207963
Date:	Tuesday, February 24, 2015 12:29:00 PM
Attachments:	image001.png
Importance:	High

Dear. Mr. Sterling,

We are referring to your NDA 207963. The following Information Request is needed to continue reviewing your application:

You have not provided adequate biowaiver information demonstrating that the PK profile data of your proposed and reference listed drug products would be similar despite the differences in the inactive ingredients. To support the approval of the biowaiver, submit a justification and evidence that the absence of disodium edetate and citrate buffer and the differences, if any, in pH and osmolality do not affect the pharmacokinetics of your proposed drug product compared to that of the reference drug product. You may use literature references to support your justification.

You are reminded to respond to the previous information request (October 27, 2014) on 1) the osmolality, pH values, and the analytical procedure/s used to measure them and 2) a justification for the absence of mannitol for your proposed drug product.

We request the needed data be submitted by COB March 06, 2015.

Please let me know if you have any questions/concerns. Also, please confirm the receipt of this email.

Thanks,

Laya Keyvan, MS, MBA
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-4598
Email: laya.keyvan@fda.hhs.gov

OFFICE OF PHARMACEUTICAL QUALITY

Laya Keyvan -A

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Laya Keyvan -A, 0.9.2342.19200300.100.1.1=2001367756
Date: 2015.02.27 13:37:20 -05'00'

From: Keyvan, Laya
To: "jsterling@lexela.us"
Subject: Information Request for NDA 207963
Date: Wednesday, January 28, 2015 2:38:00 PM
Importance: High

Dear Mr. Sterling,

I am contacting you in regards to NDA 207963. We have the following Information Request. Please provide the information to the Agency by February 28, 2015.

Please provide the following information or a reference to its location in NDA 207963:

1. *A statement as to whether or not the drug product will be* (b) (4)
2. *Confirmation that the* (b) (4) *container closure integrity test was conducted on containers exposed to* (b) (4)
3. *The maximum* (b) (4) *for the compounded drug product* (b) (4)
4. *The* (b) (4) *used to monitor the compounded drug product.*
5. (b) (4)

Please let me know if you have any questions or concerns,

Laya Keyvan, MS, MBA
Product Quality Regulatory Project Manager
Office of New Drug Quality Assessment (ONDQA)
Center for Drug Evaluation and Research
Food and Drug Administration
Email: laya.keyvan@fda.hhs.gov
Phone: 240-402-4598

Laya Keyvan -A

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Laya Keyvan -A, 0.9.2342.19200300.100.1.1=2001367756
Date: 2015.03.17 11:34:38 -04'00'

From:	Carr, James
To:	"Jonathan Sterling"
Cc:	Brancazio, Matthew (FDA); Phanesh Koneru; LCDR R. Wes Ishihara
Subject:	RE: NDA 207963 Request for Guidance
Date:	Monday, December 29, 2014 10:59:00 AM

Mr. Sterling,

We refer to your email dated December 5, 2014 the FDA provides the following guidance:
When an original application is submitted to the agency for review, we generally assume that you believe we can approve the application as submitted (i.e., the application is complete). However, you may submit an amendment to an application that has been filed but is not yet approved. Please note that upon receipt of an amendment we will assess whether we will review that amendment or defer the review until a subsequent review cycle. If we decide to review the amendment and the submission constitutes a major amendment, we may extend the review cycle by 3 months. Alternatively, you may choose to submit a CMC supplement following approval of your NDA (should it be approved).

Jay

James B Carr, MPAS, PA-C
LCDR, US Public Health Service
Regulatory Health Project Manager
CDER/OND/ODEIII
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

(240) 402-6624 (office)
(301) 796-9904 (fax)
James.Carr@fda.hhs.gov

-----Original Message-----
From: Jonathan Sterling [mailto:jsterling@exela.us]
Sent: Friday, December 05, 2014 2:41 PM
To: Carr, James
Cc: Brancazio, Matthew (FDA); Phanesh Koneru
Subject: RE: NDA 207963 Request for Guidance

James and Matt

As you may have observed in our NDA for Palonosetron Hydrochloride Injection, Exela included three lots of drug product that were pH adjusted (XLNC1306, XLNC1307, and XLNC1308) and one lot of drug product that was not pH adjusted (XLNB1421). At the time of filing, 6 months stability data and summary tables at accelerated (b) (4)

Since filing, additional data for all four (4) lots have been generated. Specifically, 6 months stability data at accelerated (40C ± 2C, 75 ± 5% RH), and 6 months stability at recommended labeled storage (25C ± 2C, 60% ± 5% RH conditions for NDA stability batch XLNB1421. Based on the observed data from this stability lot, the exclusion of the pH adjusters, sodium hydroxide and/or hydrochloric acid, has not affected the stability of the drug product formulation, evidenced by the inter and intra lot stability data compared to the three lots containing a pH adjuster.

Additionally, the stability data supports narrowing the pH specification range from (b) (4) (current) to 6.5 - 8.(b) (4) (proposed).

Since it is desirable to minimize the number of ingredients in a drug product formulation, Exela suggests the exclusion of pH adjusters from this formulation. Therefore, Exela would like to submit a revised proposed commercial batch record removing the pH adjusters from the formulation and process as well as a revised drug product specification with the tightened pH range. Please advise the best path to submit the proposed commercial batch record and revised drug product specification to the filed NDA.

Thanks in advance for your assistance and support of this project.

JES

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/s/

JAMES B CARR
12/29/2014

From:	Carr, James
To:	"Jonathan Sterling"
Cc:	CDR Matt Brancazio; LCDR James Carr
Subject:	NDA 207963 palonosetron hydrochloride injection labeling revisions
Date:	Wednesday, December 10, 2014 12:14:00 PM
Attachments:	Palenosetron.1.14.1.2.7-PI clean.docx Palenosetron.1.14.1.2.7-PI revised.pdf image001.png

Dear Mr. Sterling,

Please refer to your New Drug Application (NDA) dated August 7, 2014, received August 15, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for palonosetron hydrochloride injection, 0.125 mg/mL. Please see the attached tracked and clean versions of our proposed changes.

We request that you resubmit labeling that addresses these issues by no later than January 7, 2015.

Respectfully,

Jay

James B Carr, MPAS, PA-C
LCDR, US Public Health Service
Regulatory Health Project Manager
CDER/OND/ODEIII
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

(240) 402-6624 (office)
(301) 796-9904 (fax)
James.Carr@fda.hhs.gov

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JAMES B CARR
12/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207963

INFORMATION REQUEST

Exela Pharma Sciences, LLC
Attention: Jonathan E. Sterling
Vice President of Quality, Regulatory and Product Development
1325 William White Place NE P.O. Box 818
Lenoir, NC 28645

Dear Mr. Sterling:

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

We also refer to your June 15, 2015 submission, containing your new drug application.

We are reviewing the Microbiology sections of your submission and have the following comments and information requests. We request a prompt written response by November 15, 2015 in order to continue our evaluation of your NDA.

We acknowledge your commitment to conduct bioburden and endotoxins studies on the bulk drug product (b) (4)

If you have any questions, please contact me, at (240) 402-5826 or truong.quach@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Truong Quach, Pharm. D.

Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Truong Quach -S

Digitally signed by Truong Quach -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Truong Quach -S, 0.9.2342.19200300.100.1.1=2001511949
Date: 2015.11.09 08:20:14 -05'00'

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207963

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Exela Pharma Sciences, LLC
Attention: Jonathan E. Sterling
Vice President of Quality, Regulatory and Product Development
1325 William White Place NE P.O. Box 818
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your New Drug Application (NDA) dated August 7, 2014, received August 15, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for palonosetron hydrochloride injection, 0.125 mg/mL.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is June 15, 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 commitment requests by May 18, 2015.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Provide the proposed drug product's and listed drug product's osmolality and pH values and the analytical procedure/s used to measure them.
2. Provide justification demonstrating that the absence of mannitol in the proposed product does not impact the bioavailability of the drug.
3. Provide a clinical overview in section 2.5 of the eCTD. The clinical overview should include high level summary information for the listed drug identified in your 505(b)(2) application [NDA 021372: Aloxi (palonosetron hydrochloride) injection]. This can be obtained from the listed drug approval history as well as the approved full prescribing information. Additional relevant information, including safety information, can also be obtained from published literature, as appropriate. The clinical overview should also include the differences between the proposed formulation and the listed drug formulation and any data that indicate that these differences in formulation will not impact safety or efficacy of the proposed product. Specifically, provide a review of intravenous products (not limited to palonosetron) with comparable formulation characteristics (no tonicity agent and similar pH) and their associated local infusion site safety profile. A summary of the relevant findings from the local irritation study, EPS-2014-001, should also be included.
4. Provide justification that the design (including sample size and choice of comparator) and results of EPS-2014-001 support that removal of the tonicity agent (mannitol) and/or changes in pH will not affect the safety of the proposed product. Provide any references for previous publications of local irritation studies that you used to guide the design of your study. This can be included in Section 2.5, Clinical Overview, described above.
5. Provide narratives for all patients who experienced phlebitis and/or local irritation, as assessed by the investigator in Study EPS-2014-001.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. 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.

During our preliminary review of your submitted labeling, we have identified labeling issues and have labeling comments or questions in the attached labeling. Please refer to the attached labeling.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by November 4, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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.

Because none of these criteria apply to your application, you are exempt from this requirement.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Because this application does not trigger PREA, we will not review your waiver request.

If you have any questions, call James Carr, Regulatory Project Manager, at (240) 402-6624.

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(s):
Content of Labeling

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DONNA J GRIEBEL
10/27/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207963

NDA ACKNOWLEDGEMENT
USER FEES RECEIVED

Exela Pharma Sciences, LLC
Attention: Jonathan E. Sterling
Vice President of Quality, Regulatory and Product Development
1325 William White Place NE
P.O. Box 818
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for palonosetron hydrochloride injection, 0.125 mg/mL.

You were notified in our letter dated August 14, 2014, that your application was not accepted for filing due to non-payment of fees. This is to inform you that the Agency has received or waived all required fees and your application has been accepted as of August 15, 2014.

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 14, 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 cited above should be included 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

If you have any questions, contact Mary Chung, Regulatory Project Manager, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Brian K. 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
08/29/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207963

UNACCEPTABLE FOR FILING

Exela Pharma Sciences
Attention: Jonathan E. Sterling
Vice President of Quality, Regulatory & Product Development
1325 William White Place NE
P.O. Box 818
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your New Drug Application dated August 7, 2014, received August 8, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for palonosetron hydrochloride injection, 0.125 mg/mL.

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 979107
St. Louis, MO 63197-9000

Checks sent by courier should be addressed to:

U.S. Bank
Attention: Government Lockbox 979107
1005 Convention Plaza
St. Louis, MO 63101

When submitting payment for an application fee, include the User Fee I.D. Number, the Application number, and a copy of the user fee coversheet (Form 3397) with your application fee payment. When submitting payment for previously unpaid product and establishment fees, please include the Invoice Number(s) for the unpaid fees and the summary portion of the invoice(s) with your payment. The FDA P.O. Box number (P.O. Box 979107) should be included on any check you submit.

The receipt date for this submission (which begins the review for filability) will be the date the review division is notified that payment has been received by the bank. Please notify the regulatory project manager indicated below when the appropriate user fees have been sent.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions 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

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 wish to send payment by wire transfer, or if you have any other user fee questions, please call the Prescription Drug User Fee staff at 301-796-7900.

If you have any questions regarding this application, contact me at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Mary Chung, PharmD.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

MARY H CHUNG
08/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 116583

MEETING PRELIMINARY COMMENTS

Exela Pharma Sciences, LLC
Attention: Jonathan E. Sterling
Vice President of Quality, Regulatory & Product Development
1325 William White Place NE
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Palonosetron Hydrochloride Injection, 0.125 mg/mL.

We also refer to your September 18, 2012, correspondence, received September 21, 2012, requesting a meeting to discuss your development program and plan to file a NDA under the 505(b)(2) regulatory pathway.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-IND
Meeting Date and Time:	December 5, 2012; 12:00PM – 1:00PM EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	PIND 116583
Product Name:	Palonosetron Hydrochloride Injection, 0.125 mg/mL
Indication:	1) Moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses (CINV (b) (4)) 2) Highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses (CINV (b) (4))
Sponsor/Applicant Name:	Exela Pharma Sciences, LLC

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for December 5, 2012 from 12:00PM to 1:00PM EST between Exela Pharma Sciences, LLC and the Division of Gastroenterology and Inborn Errors Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

On September 18, 2012, Exela Pharma Sciences submitted a Type B, pre-IND meeting request to discuss their development plans for palonosetron hydrochloride injection, 0.125 mg/mL. The sponsor's meeting request included their background package. FDA granted the meeting in the correspondence dated October 11, 2012. Exela intends to submit their application via the 505(b)(2) regulatory pathway and rely on the list drug application for NDA 021372 Aloxi (palonosetron hydrochloride) injection.

As described in the background package, the differences between the sponsor's palonosetron hydrochloride injection and the reference Aloxi injection are:

- Exela's product contains 0.125 mg palonosetron base/mL, whereas Aloxi injection contains 0.025 mg palonosetron base/mL
- Exela's product does not contain (b) (4) mannitol (b) (4) disodium EDTA), or (b) (4) citrate buffer (b) (4) which are all components of Aloxi injection
- Exela's product has a pH of (b) (4) to 8.5 whereas Aloxi injection has a pH of 4.5 to 5.5

2.0 DISCUSSION

Question 1: Does the Agency concur that for Exela's Palonosetron Hydrochloride Injection, the appropriate Reference Listed Drug (RLD) is ALOXI Injection (NDA # N021372)?

- *ALOXI (palonosetron hydrochloride) injection (0.25 mg palonosetron base/5 mL, 0.05 mg/mL) of (b) (4) contains; 0.25 mg palonosetron base as 0.28 mg palonosetron hydrochloride, (b) (4) mg mannitol, disodium edetate and citrate buffer in water for intravenous administration. The pH of the solution in the vials is 4.5 to 5.5*
- *Exela's Palonosetron Hydrochloride Injection (0.25 mg palonosetron base/2 mL, 0.125 mg/mL) will contain; 0.25 mg palonosetron base as 0.28 mg palonosetron hydrochloride, in water for intravenous administration. The pH of the solution in the vials is (b) (4) to 8.5*

FDA Response:
The Agency typically does not advise a sponsor on the selection of a particular listed drug that may be relied upon to support approval of a proposed product. A sponsor interested in submitting a 505(b)(2) application that relies upon the Agency's finding of safety and/or effectiveness for a listed drug should determine which listed drug(s) is/are the most appropriate for their development plan.

Question 2: Is the Agency in agreement with the 505(b)(2) pathway for Exela's Palonosetron Hydrochloride Injection?

- *Exela proposes to rely on data in the public domain to satisfy nonclinical requirements and to provide information about the clinical pharmacology efficacy and safety of ALOXI Injection for Moderately emetogenic cancer chemotherapy (prevention of acute and delayed nausea and vomiting associated with initial and repeat courses) and Highly*

emetogenic cancer chemotherapy (prevention of acute nausea and vomiting associated with initial and repeat courses). Specifically, Exela intends to use ALOXI Injection as the Reference Listed Drug. Exela believes that the distinct formulation differences between ALOXI Injection and Exela's Palonosetron Hydrochloride Injection identified above will make Exela's filing ineligible for an ANDA submission under 505(j) and hence, it proposes to submit NDA under 505(b)(2) as a pathway for its Palonosetron Hydrochloride Injection.

FDA Response:
A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf . In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.pdf) .

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. Alternatively, you may request a biowaiver under 21 CFR 320.22.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate. Copies of the articles must be included and any proprietary names in those reports identified. If a product is identified by proprietary name and the information in the literature article is required for approval, including for the labeling, then that product must be included in the list of products relied upon for approval and the required patent notification and certification procedures followed.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely

upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

Please clarify what you mean by "data in the public domain."

Question 3: Does the FDA agree that the pharmacokinetics, efficacy, and safety data in the public domain and from the approved labeling of ALOXI Injection (NDA # 021372) support the efficacy and safety of Exela's Palonosetron Hydrochloride Injection (b) (4)?

- *Exela's Palonosetron Hydrochloride Injection and ALOXI Injection both contain 0.25 mg palonosetron base per vial; however, the concentration of palonosetron per mL of liquid formulation is different. Exela's Palonosetron Hydrochloride Injection has a concentration of 0.125 mg/mL, whereas ALOXI Injection has a concentration of 0.025 mg/mL. Due to the concentration differences, the proposed fill volume of Exela's Palonosetron is 2 mL per vial compared to ALOXI Injection with a fill volume of 5 mL per vial.*
- *Exela's Palonosetron Hydrochloride does not contain a tonicity agent, a chelating agent, or a buffer; therefore, is different from ALOXI Injection. Exela's Palonosetron Hydrochloride Injection does not contain (b) (4) whereas ALOXI Injection contains mannitol. Exela's Palonosetron Hydrochloride Injection does not contain (b) (4) (b) (4) whereas ALOXI Injection contains disodium EDTA, (b) (4) Exela's Palonosetron Hydrochloride Injection does not contain (b) (4) ALOXI Injection contains a citrate buffer. Exela's Palonosetron Hydrochloride Injection has a pH of (b) (4) to 8.5, whereas ALOXI Injection has a pH of 4.5 to 5.5. From the available literature, Exela is unable to find any data or report that indicate that these differences in formulation between ALOXI Injection and Exela's Palonosetron Hydrochloride Injection will affect safety or efficacy of Exela's Palonosetron Hydrochloride Injection. Exela therefore requests that the FDA determine that no pharmacokinetic studies or clinical studies are needed to demonstrate efficacy and safety of Exela's Palonosetron Hydrochloride Injection.*

FDA Response:
Removal of [redacted] mannitol and/or changes in pH may affect safety (i.e. injection site reactions). You will need to adequately justify that these changes will not affect the safety of the proposed product. This may require the submission of additional safety data.

Question 4: Does the FDA agree that no pediatric studies will be required and that PREA has been addressed?

- [redacted] *did not conduct studies in patients below the age of 18 years; however, such studies may have been planned. If data from such studies are available to the FDA before the approval of Exela's Palonosetron Hydrochloride Injection, Exela requests that the FDA determine that no clinical studies in the pediatric population are needed for Exela's Palonosetron Hydrochloride Injection.*

FDA Response:
If your application is accepted for filing, you may be exempt from PREA requirements as your product does not appear to propose new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration as compared to the listed drug.

Question 5: Because Exela's Palonosetron Hydrochloride Injection will be therapeutically equivalent and pharmaceutically equivalent does the agency agree that Exela's product will be rated as "AP" to [redacted] ALOXI (palonosetron hydrochloride) Injection?

- *Exela's Palonosetron Hydrochloride Injection will have the same active ingredient, the same dosage form (i.e., solution), and the same route of administration. Moreover, Exela's product will be labeled for* [redacted] *ALOXI Injection and administered to the patient the same way. As discussed above, Exela submits that its proposed product is therapeutically equivalent to ALOXI Injection. Accordingly, Exela requests that its product be granted an "AP" rating upon approval.*

FDA Response:
Therapeutic equivalence evaluations are made after approval of an application. However, please note that according to the Preface of the Orange Book, Section 1.2, therapeutic equivalents must be pharmaceutical equivalents and pharmaceutical equivalents must be identical in strength or concentration:
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf .

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/s/

JAGJIT S GREWAL
11/30/2012

For Internal Use Only

Meeting Cancellation Form

(Use this form to cancel a meeting that was granted and scheduled after which time the sponsor or FDA has subsequently cancelled.)

Please remember to update the Meeting Status field in DARRTS for this cancellation.

Complete the information below and check form into DARRTS.

Application Type	☒P-IND ☐ IND ☐ NDA/sNDA
Application Number	PIND 116583
DATE Meeting Cancelled (per communication with requester)	December 3, 2012
Scheduled Meeting Date	December 5, 2012
Reason for Cancellation	Reference is made to FDA's correspondence dated October 11, 2012, granting Exela Pharma Sciences September 18, 2012 Type B, pre-IND meeting request. Further reference is made to FDA's preliminary responses dated November 30, 2012. The Type B meeting was scheduled to be held on December 5, 2012. Per discussion with James Sterling (Vice President of Quality, Regulatory, & Product Development) on December 3, 2012, Exela has accepted FDA's preliminary responses in lieu of holding the scheduled meeting. Therefore, the Type B meeting has been cancelled. Exela will submit formal correspondence to the PIND file noting cancellation of the meeting.
Project Manager	Jagjit Grewal, M.P.H.

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

/s/

JAGJIT S GREWAL
12/04/2012