APPLICATION NUMBER:

209935Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
Debarment Certification

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

[Signature]

Concetta Freund, Sr. Global Program Regulatory Manager
Drug Regulatory Affairs

[Signature]

Date

Jan 25, 2017
# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>209935</th>
<th>NDA Supplement #</th>
<th>BLA #</th>
<th>BLA Supplement #</th>
<th>If NDA, Efficacy Supplement Type: (an action package is not required for SE8 or SE9 supplements)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary Name:</td>
<td>Kisqali Femara CO-PACK</td>
<td>Established/Proper Name:</td>
<td>ribociclib and letrozole</td>
<td>Applicant:</td>
<td>Novartis Pharmaceuticals Corporation</td>
</tr>
<tr>
<td>Dosage Form:</td>
<td>Tablets</td>
<td>Agent for Applicant (if applicable):</td>
<td></td>
<td>Division:</td>
<td>DOP1</td>
</tr>
</tbody>
</table>

### For ALL 505(b)(2) applications, two months prior to EVERY action:

- Review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance.
- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)

- No changes
- New patent/exclusivity *(notify CDER OND IO)*

**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.

### Actions

- Proposed action
- User Fee Goal Date is November 30, 2017

### Previous actions (specify type and date for each action taken)

- None

### Co-Packaged NDA Type 4

- New Combination

---

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).

3. 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.
Review priority:  ✗ Standard (Expedited)  □ Priority

Chemical classification (new NDAs only):  (confirm chemical classification at time of approval)

□ Fast Track  □ Rx-to-OTC full switch
□ Rolling Review  □ Rx-to-OTC partial switch
□ Orphan drug designation  □ Direct-to-OTC
✓ Breakthrough Therapy designation

(Note: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the “RPM BT Checklist for Considerations after Designation Granted” for other required actions: CST SharePoint)

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

BLAs: Subpart E
- □ Accelerated approval (21 CFR 601.41)
- □ Restricted distribution (21 CFR 601.42)

Subpart H
- □ Approval based on animal studies

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)  □ Yes  □ No
- □ Public communications (approvals only)
  - □ Office of Executive Programs (OEP) liaison has been notified of action  □ Yes  □ No
  - □ Indicate what types (if any) of information were issued  □ None  □ FDA Press Release  □ FDA Talk Paper  □ CDER Q&As  □ Other

Exclusivity

- □ Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?  □ No  □ 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.
  □ Verified  □ 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)  □ Included
- □ Documentation of consent/non-consent by officers/employees  □ Included
<table>
<thead>
<tr>
<th>Action Letters</th>
<th>Approved Date 5-4-17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copies of all action letters (including approval letter with final labeling)</td>
<td></td>
</tr>
</tbody>
</table>

### Labeling

<table>
<thead>
<tr>
<th>Package Insert (write submission/communication date at upper right of first page of PI)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)</td>
<td>Included 4-24-17</td>
</tr>
<tr>
<td>▶ Original applicant-proposed labeling</td>
<td>Included 1-30-17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)</td>
<td>Included 4-24-17</td>
</tr>
<tr>
<td>▶ Original applicant-proposed labeling</td>
<td>Included 1-30-17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Most-recent draft labeling</td>
<td>Included 4-28-17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proprietary Name</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Acceptability/non-acceptability letter(s) (indicate date(s))</td>
<td>3-22-17 (Letter)</td>
</tr>
<tr>
<td>▶ Review(s) (indicate date(s))</td>
<td>3-10-17 (Review)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Labeling reviews (indicate dates of reviews)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RPM: ☒ 3-29-17</td>
<td></td>
</tr>
<tr>
<td>DMEPA: ☒ 3-17-17, 3-29-17</td>
<td></td>
</tr>
<tr>
<td>DMPP/PLT (DRISK): ☒ 4-14-17</td>
<td></td>
</tr>
<tr>
<td>OPDP: ☒ 4-13-17</td>
<td></td>
</tr>
<tr>
<td>SEALD: ☒ None</td>
<td></td>
</tr>
<tr>
<td>CSS: ☒ None</td>
<td></td>
</tr>
<tr>
<td>Product Quality: ☒ 4-30-17</td>
<td></td>
</tr>
<tr>
<td>Other: ☒ None</td>
<td></td>
</tr>
</tbody>
</table>

### Administrative / Regulatory Documents

<table>
<thead>
<tr>
<th>RPM Filing Review/Memo of Filing Meeting (indicate date of each review)</th>
<th>3-29-17</th>
</tr>
</thead>
<tbody>
<tr>
<td>All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee</td>
<td>☒ Not a (b)(2)</td>
</tr>
</tbody>
</table>

| NDAs/NDA supplements only: Exclusivity Summary (signed by Division Director) | Completed (Do not include) |

<table>
<thead>
<tr>
<th>Application Integrity Policy (AIP) Status and Related Documents</th>
<th><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Applicant is on the AIP</td>
<td>☒ Yes ☒ No</td>
</tr>
</tbody>
</table>

---

4 Filing reviews for scientific disciplines are NOT required to be included in the action package.
This application is on the AIP
- If yes, Center Director’s Exception for Review memo (indicate date)
  □ Yes  □ No
- If yes, OC clearance for approval (indicate date of clearance communication)
  □ Not an AP action

Pediatrics (approvals only)
- Date reviewed by PeRC  4-5-17
  If PeRC review not necessary, explain: ________

Breakthrough Therapy Designation
□ N/A

- Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 8-2-16
- CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (include only the completed template(s) and not the meeting minutes) 8-2-16
- CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (include only the completed template(s) and not the meeting minutes)

(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)

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, Formal Dispute Resolution Request decisional letters, etc.) (do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)
4-26 x2, 4-17, 4-11, 4-10, 4-7, 4-6, 3-31 x2, 3-29, 3-22, 3-20, 3-17, 3-3, 2-22 x3, 2-9, 2-8

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)
N/A

Minutes of Meetings
- If not the first review cycle, any end-of-review meeting (indicate date of mtg) □ N/A
- Pre-NDA/BLA meeting (indicate date of mtg) □ WRO 11-16-16
- EOP2 meeting (indicate date of mtg) □ No mtg
- Mid-cycle Communication (indicate date of mtg) □ N/A
- Late-cycle Meeting (indicate date of mtg) □ N/A
- Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (indicate dates of mtgs)
  □ N/A
- Advisory Committee Meeting(s) □ No AC meeting
- Date(s) of Meeting(s)

Decisional and Summary Memos
- Office Director Decisional Memo (indicate date for each review) □ None
- Division Director Summary Review (indicate date for each review) □ 5-2-17
- Cross-Discipline Team Leader Review (indicate date for each review) □ None
- PMR/PMC Development Templates (indicate total number) □ PMC 1

Clinical

Reference ID: 4093693
<table>
<thead>
<tr>
<th>Section</th>
<th>Reviews/Inspections</th>
<th>Date/Location</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Reviews</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Team Leader</td>
<td>Review(s) (indicate date for each review)</td>
<td>No separate review</td>
</tr>
<tr>
<td>Clinical review(s)</td>
<td>(indicate date for each review)</td>
<td>3-6-17, 4-26-17</td>
</tr>
<tr>
<td>Social scientist review</td>
<td>(if OTC drug) (indicate date for each review)</td>
<td>None</td>
</tr>
<tr>
<td>Financial Disclosure</td>
<td>reviews(s) or location/date if addressed in another review</td>
<td>See Clinical Review</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)</td>
<td>N/A</td>
</tr>
<tr>
<td>Risk Management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REMS Documents and</td>
<td>REMS Supporting Document (indicate date(s) of submission(s))</td>
<td>N/A</td>
</tr>
<tr>
<td>REMS Memo(s) and</td>
<td>letter(s) (indicate date(s))</td>
<td>N/A</td>
</tr>
<tr>
<td>Risk management</td>
<td>review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)</td>
<td>None</td>
</tr>
<tr>
<td>OSI Clinical</td>
<td>Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)</td>
<td>None requested</td>
</tr>
<tr>
<td>Microbiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Microbiology</td>
<td>Review(s) (indicate date for each review)</td>
<td>No separate review</td>
</tr>
<tr>
<td>Statistical</td>
<td>Division Director Review(s) (indicate date for each review)</td>
<td>No separate review</td>
</tr>
<tr>
<td>Statistical</td>
<td>Team Leader Review(s) (indicate date for each review)</td>
<td>No separate review</td>
</tr>
<tr>
<td>Statistical</td>
<td>Review(s) (indicate date for each review)</td>
<td>None</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>Division Director Review(s) (indicate date for each review)</td>
<td>No separate review</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>Team Leader Review(s) (indicate date for each review)</td>
<td>No separate review</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>review(s) (indicate date for each review)</td>
<td>3-13-17, 3-30-17</td>
</tr>
<tr>
<td>OSI Clinical</td>
<td>Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)</td>
<td>None requested</td>
</tr>
</tbody>
</table>

5 For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).
### Nonclinical

- **Pharmacology/Toxicology Discipline Reviews**
  - ADP/T Review(s) *(indicate date for each review)*
    - No separate review
  - Supervisory Review(s) *(indicate date for each review)*
    - No separate review
  - Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*
    - 4-21-17
  - Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*
    - None
  - Statistical review(s) of carcinogenicity studies *(indicate date for each review)*
    - No carc
  - ECAC/CAC report/memo of meeting
    - None
    - Included in P/T review, page
  - OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*
    - None requested

### Product Quality

- **Product Quality Discipline Reviews**
  - Tertiary review *(indicate date for each review)*
    - None
  - Secondary review (e.g., Branch Chief) *(indicate date for each review)*
    - None
  - Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*
    - 3-8-17, 4-30-17
  - Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*
    - None
  - Environmental Assessment (check one) (original and supplemental applications)
    - Categorical Exclusion *(indicate review date); all original applications and all efficacy supplements that could increase the patient population)*
      - See CMC Review
    - Review & FONSI *(indicate date of review)*
    - Review & Environmental Impact Statement *(indicate date of each review)*

### Facilities Review/Inspection

- Facilities inspections *(indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter)* *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*
  - Acceptable 3-24-17
  - Re-evaluation date:
    - Withhold recommendation
    - Not applicable

---

6 Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.
# Day of Approval Activities

<table>
<thead>
<tr>
<th>Activity</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>For all 505(b)(2) applications:</td>
<td></td>
</tr>
<tr>
<td>- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</td>
<td></td>
</tr>
<tr>
<td>- Finalize 505(b)(2) assessment</td>
<td></td>
</tr>
<tr>
<td>- For Breakthrough Therapy (BT) Designated drugs:</td>
<td></td>
</tr>
<tr>
<td>- Notify the CDER BT Program Manager</td>
<td></td>
</tr>
<tr>
<td>- For products that need to be added to the flush list (generally opioids):</td>
<td></td>
</tr>
<tr>
<td>- Notify the Division of Online Communications, Office of Communications</td>
<td></td>
</tr>
<tr>
<td>- Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</td>
<td></td>
</tr>
<tr>
<td>- If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter</td>
<td></td>
</tr>
<tr>
<td>- Ensure that proprietary name, if any, and established name are listed in the Application Product Names section of DARRTS, and that the proprietary name is identified as the “preferred” name</td>
<td></td>
</tr>
<tr>
<td>- Ensure Pediatric Record is accurate</td>
<td></td>
</tr>
<tr>
<td>- Send approval email within one business day to CDER-APPROVALS</td>
<td></td>
</tr>
</tbody>
</table>

- Check for new patent/exclusivity (Notify CDER OND IO)
- Send email to CDER OND IO
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

------------------------------------------
AMY R TILLEY
05/04/2017
Connie, on second thought, to make sure we attach all 17 of the agreed upon carton and container labels please submit all your final carton and container labels in one submission. Kindly let me know once you have submitted them through the Gateway so I can be on the lookout for them.

Many thanks,
Amy

---

Connie, thank you for the confirmation on the carton and container labels. I seem to remember that some of the NDC codes needed to be changed, as well as a “s” being included in the word Tablet’s”. I want to be sure the labels all have the correct NDC codes as I am using all the March 27th labels except for the 4 that were re-submitted on April 24th.

There will be no Press Release or Burst for this NDA.

Thanks.
Amy

---

HI Amy,

Thanks for your message and for your availability to discuss via phone.

I confirm that there were 4 carton labels updated in the 04/24/2017 submission (3 trade cartons, and one physician sample). Also am confirming that the digits at the end of the PDFs can be used for tracking purposes (these are our production codes). So, for example – the PDF ending in “8006” would be replacing the prior “8006” submitted on March 27th.

You are correct in that there are a total of 17 carton and container labels for the co-pack. I wanted to highlight that there was one additional PDF submitted in the original sequence 0000 (so there were 18 files then), which is basically just a filler for the 200 mg co-pack presentation (i.e. there is no regulatory text on this, but we wanted to include for transparency purposes). The production codes were not assigned at the time of original submission, but in case you need it, the filler was
Connie, this email is a follow up to my vm from a few moments ago. Upon my review of the April 24, 2017, submission of the agreed upon PI/PPI and carton and container labels it appears that the 200 mg 600 mg sample carton 118006 and 200 mg 600 mg trade carton 118000 are duplicates of one another. I thought in an earlier email that you stated there would only be 3 revised labels but 4 were submitted. Perhaps an additional label was sent erroneously.

Please confirm which revised labels should have been sent in the April 24, 2017, submission.

Your prompt response is greatly appreciated.

Regards,

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------------------------------------
AMY R TILLEY
04/26/2017
Connie, this email is a follow up to my vm from a few moments ago. Upon my review of the April 24, 2017, submission of the agreed upon PI/PPI and carton and container labels it appears that the 200 mg 600 mg sample carton 118006 and 200 mg 600 mg trade carton 118000 are duplicates of one another. I thought in an earlier email that you stated there would only be 3 revised labels but 4 were submitted. Perhaps an additional label was sent erroneously.

Please confirm which revised labels should have been sent in the April 24, 2017, submission.

Your prompt response is greatly appreciated.

Regards,

Amy R. Tilley
Regulatory Project Manager
Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------
AMY R TILLEY
04/26/2017
I forgot to attach the PI document only.

amy

Connie, my apologies as I should have deleted the PPI that was attached to the PI prior to sending you this IR. Please see the above PI (with PPI deleted) for Novartis’ review. Please review the PPI that was sent in my previous email that was attached as a separate Word document.

Kindly confirm receipt of this email.

Regards.
Amy

Connie, the purpose of this email is to send you the attached FDA Revised PI (one minor revision in Section 11) and PPI for Novartis’ review.

We request your response to this email no later than 12 noon on April 24, 2017.

Regards,
Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

12 Page(s) of Draft Labeling 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/

---------------------------------------------
AMY R TILLEY
04/17/2017
Connie, the purpose of this email is to send you the attached FDA Revised PI with a few minor revisions. The PPI is still under review. As previously discussed, please email your revised PI with edits to section 16, revisions to the NDC numbers for the 600 mg and 200 co-pack cartons, and the PMC on Thursday, April 13, 2017. Please follow up with an official submission to the NDA.

Please accept the FDA revisions in the PI that you agree with or add comments should you not agree. Please keep all your revisions in tracked changes.

Regards.

Amy R. Tilley  
Regulatory Project Manager  
Center for Drug Evaluation & Research  
Office of Hematology Oncology Products  
Division of Oncology Products 1  
U.S. Food and Drug Administration  
Tel: 301-796-3994  
amy.tilley@fda.hhs.gov

---

Ok thanks Amy.

Confirming receipt.

Kind regards,

Connie

Concetta Freund, MS  
Drug Regulatory Affairs  
Novartis Pharmaceuticals Corporation  
One Health Plaza, 315  
East Hanover, NJ 07936-1080  
Office phone +1 862-778-3501  
Cell phone [redacted]
Connie, just a heads up today I will be sending you the revised PI with one revision and a few minor format changes. We request you incorporate these changes in the PI you send to us on Thursday.

Thanks.
amy

Hi Amy,

I just wanted to provide a “heads-up” that we caught one item in section 16 of the USPI which will need a correction from our end.

The NDC numbers for the 600 mg co-pack carton configuration and the 200 mg co-pack carton configuration need to be switched from each other (the 600 mg has the 200 mg NDC number, and vice versa). I plan to submit this revised, corrected USPI, along with the PMC on Thursday.

Thanks and kind regards,
Connie

Concetta Freund, MS
Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315
East Hanover, NJ 07936-1080
Office phone +1 862-778-3501
Cell phone
connie.freund@novartis.com
www.novartis.com
Hi Amy,

Thanks again.

Attached, please find the NVS responses to the proposed USPI revisions, both in tracked changes and clean versions.

Please note that we have accepted the revisions, and propose one minor edit to the sentence in Section 6, along with some formatting edits.

I will submit this formally to NDA 209,935 on Monday.

Have a nice weekend,
Connie

Concetta Freund, MS
Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315
East Hanover, NJ 07936-1080
Office phone +1 862-778-3501
Cell phone +
connie.freund@novartis.com
www.novartis.com

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Thursday, March 30, 2017 4:40 PM
To: Freund, Connie <connie.freund@novartis.com>
Subject: TIME SENSITIVE re NDA 209935 Kisqali Femara Co-pack - FDA Revised PI only
Importance: High
Sensitivity: Confidential

Connie, the purpose of this email is to send you the attached revised NDA 209935 Kisqali Femara Co-pack PI only. Please note we are still reviewing the PPI portion of the label.

We request your emailed response by 10 am on Monday, April 10, 2017, then follow up with an official submission to the NDA.

Kindly confirm receipt of this email.

Regards,

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

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

Reference ID: 4082770
Connie, the purpose of this email is to let you know the Agency agrees with Novartis’ revisions to the PMC description. Please confirm Novartis is in agreement with the PMC description and Milestone below. If so, officially submit the PMC and Milestone to the NDA. Kindly let me know the day you plan to officially submit this information.

Demonstrate the comparability of the proposed packaging configuration to drug product packaged in the registered packaging configurations.

Submit the MVTR data and updated 3.2.P.7 as described in Section 6 of the comparability protocol (protocol referenced to NDA 20726 / S-031), and if MVTR/tablet data of the proposed packaging falls outside the range for the approved packaging, submit a stability report containing three months of accelerated stability data for one batch of drug product using the proposed 28-count packaging configuration. Submit a commitment to place the first commercial batch on long-term stability to support the 28-count bottle of Femara.

Final Report Submission: 10/2017

Regards.

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

From: Freund, Connie [mailto:connie.freund@novartis.com]
Sent: Monday, April 10, 2017 3:57 PM
To: Tilley, Amy
Subject: RE: TIME SENSITIVE re NDA 209935 Kisqali Femara Co-Pack - PMC Description and Milestone ** Novartis proposed language for consideration**

Hi Amy –

One addition – I realize I forgot the word data below (highlighted below in yellow for you).

Thanks,
Demonstrate the comparability of the proposed packaging configuration to drug product packaged in the registered packaging configurations. Submit the MVTR data and updated 3.2.P.7 as described in Section 6 of the comparability protocol (protocol referenced to NDA 20726 / S-031), and if MVTR/tablet data of proposed packaging falls outside the range for the approved packaging, submit a stability report containing three months of accelerated stability data for one batch of drug product using the proposed 28-count packaging configuration. Submit a commitment to place the first commercial batch on long-term stability to support the 28-count bottles of Femara.
From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Monday, April 10, 2017 1:12 PM
To: Freund, Connie <connie.freund@novartis.com>
Subject: RE: TIME SENSITIVE re NDA 209935 Kisqali Femara Co-Pack - PMC Description and Milestone ** Novartis proposed language for consideration**

Would you please have your revisions in tracked changes so we know exactly what you changed?

Thanks.
Amy

From: Freund, Connie [mailto:connie.freund@novartis.com]
Sent: Monday, April 10, 2017 1:01 PM
To: Tilley, Amy
Subject: RE: TIME SENSITIVE re NDA 209935 Kisqali Femara Co-Pack - PMC Description and Milestone ** Novartis proposed language for consideration**

Thanks again, Amy.

Please find a slightly re-worded PMC description below, for the Agency’s consideration. Please let me know if there are any questions.

Thanks in advance,
Connie

Concetta Freund, MS
Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315
East Hanover, NJ 07936-1080
Office phone +1 862-778-3501
Cell phone +connie.freund@novartis.com
www.novartis.com
Certainly.
Have a good weekend.

amy

Apologies – one additional question: Can we provide our response by Monday EOB?

Thanks in advance,
Connie

Thanks Amy – confirming receipt.
Connie

Concetta Freund, MS
Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315
East Hanover, NJ 07936-1080
Office phone +1 862-778-3501
Cell phone
connie.freund@novartis.com
www.novartis.com

Reference ID: 4082514
Milestone ** Novartis proposed language for consideration**

**Importance:** High

**Sensitivity:** Confidential

Connie, the purpose of this email is to respond to your revisions to the PMC. See the Agency’s revised PMC below and let me know if Novartis has any further revisions. Also, your plan to update the comparability protocol to reflect the requested changes received on April 03, 2017, under NDA 20726 is acceptable.

Submit the MVTR data and updated 3.2.P.7 as described in Section 6 of the comparability protocol (protocol referenced to NDA 20726 / S-031) with a stability report containing three months of accelerated stability data for one batch of drug product using the proposed 28-count packaging configuration (if MVTR/tablet of proposed packaging falls outside the range for the approved packaging) and demonstrating the comparability of the proposed packaging configuration to the drug product packaged in the registered packaging configurations. Submit a commitment to place the first commercial batch on long-term stability to support the long term stability of the 28-count bottles of Femara.

Regards.

Amy R. Tilley
Regulatory Project Manager
Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

---

**From:** Freund, Connie [mailto:connie.freund@novartis.com]
**Sent:** Friday, April 07, 2017 12:25 PM
**To:** Tilley, Amy
**Subject:** RE: TIME SENSITIVE re NDA 209935 Kisqali Femara Co-Pack - PMC Description and Milestone ** Novartis proposed language for consideration**

**Sensitivity:** Confidential

Dear Amy,

Thanks for this opportunity to review the Agency’s PMC language related to NDA 209,935. Please find the Novartis proposed edits below (modifications in red).

**PMC Description:**

Submit the MVTR data and updated 3.2.P.7 as described in Section 6 of the comparability protocol with a stability report (if MVTR/tablet of proposed packaging falls outside the range for the approved
packaging) and a commitment to place the first commercial batch on long-term stability (protocol referenced to NDA 20726 / S-031) to support the long term stability of the 28-count bottles of Femara.

Milestone:
Final Report Submission: 10/2017

We wanted to let the Agency know that, assuming there are no further changes requested to the comparability protocol submitted to NDA 20-726, we could submit this data package by May. If there are any requested changes, we may need to modify the final report submission date listed in the draft PMC (currently Oct 2017).
We were planning to update the comparability protocol to reflect the requested changes received on Apr 03 under NDA 20-726. Please let us know if this is acceptable.

Thank you in advance and kind regards,
Connie

Concetta Freund, MS  
Drug Regulatory Affairs  
Novartis Pharmaceuticals Corporation  
One Health Plaza, 315  
East Hanover, NJ 07936-1080  
Office phone +1 862-778-3501  
Cell phone +1 862-778-3501  
connie.freund@novartis.com  
www.novartis.com

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]  
Sent: Thursday, April 06, 2017 2:51 PM  
To: Freund, Connie <connie.freund@novartis.com>  
Subject: TIME SENSITIVE re NDA 209935 Kisqali Femara Co-Pack - PMC Description and Milestone  
Importance: High  
Sensitivity: Confidential

Connie, the purpose of this email is to send you the PMC Description and Milestone below. Please review and respond by 1 pm on Friday, April 7, 2017 via email. Once we are in agreement with the PMC Description and Milestone I will inform you when to officially submit the information to the NDA.

PMC Description:

Milestone:
Final Report Submission: 10/2017

Kindly confirm receipt of this email.

Regards.

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

-----------------------------------------------
AMY R TILLEY
04/10/2017

Reference ID: 4082514
Connie, the purpose of this email is to respond to your revisions to the PMC. See the Agency’s revised PMC below and let me know if Novartis has any further revisions. Also, your plan to update the comparability protocol to reflect the requested changes received on April 03, 2017, under NDA 20726 is acceptable.

Submit the MVTR data and updated 3.2.P.7 as described in Section 6 of the comparability protocol (protocol referenced to NDA 20726 / S-031) with a stability report containing three months of accelerated stability data for one batch of drug product using the proposed 28-count packaging configuration (if MVTR/tablet of proposed packaging falls outside the range for the approved packaging) and demonstrating the comparability of the proposed packaging configuration to the drug product packaged in the registered packaging configurations. Submit a commitment to place the first commercial batch on long-term stability to support the long term stability of the 28-count bottles of Femara.

Regards.

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

From: Freund, Connie [mailto:connie.freund@novartis.com]
Sent: Friday, April 07, 2017 12:25 PM
To: Tilley, Amy
Subject: RE: TIME SENSITIVE re NDA 209935 Kisqali Femara Co-Pack - PMC Description and Milestone ** Novartis proposed language for consideration**

Dear Amy,

Thanks for this opportunity to review the Agency’s PMC language related to NDA 209,935. Please
find the Novartis proposed edits below (modifications in red).

**PMC Description:**
Submit the MVTR data and updated 3.2.P.7 as described in Section 6 of the comparability protocol with a stability report (if MVTR/tablet of proposed packaging falls outside the range for the approved packaging) and a commitment to place the first commercial batch on long-term stability (protocol referenced to NDA 20726 / S-031) to support the long term stability of the 28-count bottles of Femara.

**Milestone:**
*Final Report Submission:* 10/2017

We wanted to let the Agency know that, assuming there are no further changes requested to the comparability protocol submitted to NDA 20-726, we could submit this data package by May. If there are any requested changes, we may need to modify the final report submission date listed in the draft PMC (currently Oct 2017).
We were planning to update the comparability protocol to reflect the requested changes received on Apr 03 under NDA 20-726. Please let us know if this is acceptable.

Thank you in advance and kind regards,
Connie

Concetta Freund, MS  
Drug Regulatory Affairs  
Novartis Pharmaceuticals Corporation  
One Health Plaza, 315  
East Hanover, NJ 07936-1080  
Office phone +1 862-778-3501  
Cell phone + (b) (6)  
connie.freund@novartis.com  
www.novartis.com

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]  
Sent: Thursday, April 06, 2017 2:51 PM  
To: Freund, Connie <connie.freund@novartis.com>  
Subject: TIME SENSITIVE re NDA 209935 Kisqali Femara Co-Pack - PMC Description and Milestone  
Importance: High  
Sensitivity: Confidential

Connie, the purpose of this email is to send you the PMC Description and Milestone below. Please review and respond by 1 pm on Friday, April 7, 2017 via email. Once we are in agreement with the PMC Description and Milestone I will inform you when to officially submit the information to the NDA.

PMC Description:
Submit the final report with the stability commitment and data from the comparability studies (protocol referenced to NDA 20726 / S-031) to support the long term stability of the 28-count bottles of Femara.

Milestone:
Final Report Submission: 10/2017

Kindly confirm receipt of this email.

Regards.

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------------------------
AMY R TILLEY
04/07/2017
Connie, the purpose of this email is to send you the PMC Description and Milestone below. Please review and respond by 1 pm on Friday, April 7, 2017 via email. Once we are in agreement with the PMC Description and Milestone I will inform you when to officially submit the information to the NDA.

PMC Description:
Submit the final report with the stability commitment and data from the comparability studies (protocol referenced to NDA 20726 / S-031) to support the long term stability of the 28-count bottles of Femara.

Milestone:
Final Report Submission: 10/2017

Kindly confirm receipt of this email.

Regards.

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

Reference ID: 4081080
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

______________________________________________
AMY R TILLEY
04/06/2017

Reference ID: 4081080
Connie, the purpose of this email is to send you the attached revised NDA 209935 Kisqali Femara Co-pack PI only. Please note we are still reviewing the PPI portion of the label.

We request your emailed response by **10 am on Monday, April 10, 2017**, then follow up with an official submission to the NDA.

-  

Kindly confirm receipt of this email.

Regards,

**Amy R. Tilley**

Regulatory Project Manager

Center for Drug Evaluation & Research  
Office of Hematology Oncology Products  
Division of Oncology Products 1  
U.S. Food and Drug Administration  
Tel: 301-796-3994  
amy.tilley@fda.hhs.gov

---

23 Page(s) of Draft Labeling 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/

-----------------------------------
AMY R TILLEY
03/31/2017
There are no further comments on the carton and container labeling.

---

Thanks again, Amy.

We were wondering if there would be any forthcoming comments on the carton and container labeling, or if the Novartis-agreed labeling submitted on Monday is still under review?

Thanks for your insight on this aspect.

Kind regards,
Connie

Concetta Freund, MS
Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315
East Hanover, NJ 07936-1080
Office phone +1 862-778-3501
Cell phone [b (b)]
connie.freund@novartis.com
www.novartis.com

---

Connie, the purpose of this email is to send you the attached revised NDA 209935 Kisqali Femara Co-pack PI only. Please note we are still reviewing the PPI portion of the label.

We request your emailed response by 10 am on Monday, April 10, 2017, then follow up with an official submission to the NDA.

Kindly confirm receipt of this email.
Regards.

Amy R. Tilley  
Regulatory Project Manager

Center for Drug Evaluation & Research  
Office of Hematology Oncology Products  
Division of Oncology Products 1  
U.S. Food and Drug Administration  
Tel: 301-796-3994  
amy.tilley@fda.hhs.gov

Reference ID: 4078450
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------------------------------

AMY R TILLEY
03/31/2017
NDA 209935

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Novartis Pharmaceuticals Corporation
Attention: Concetta Freund
Senior Global Program Regulatory Manager
One Health Plaza
East Hanover, NJ  07936-1080

Dear Ms. Freund:

Please refer to your New Drug Application (NDA) dated January 30, 2017, received January 30, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Kisqali Femara CO-PACK (ribociclib and letrozole) Tablets, 200 mg (ribociclib); 2.5 mg (letrozole).

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 January 30, 2018. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm).

However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

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 November 9, 2017. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests.

Reference ID: 4076446
In addition, the planned date for our internal mid-cycle review meeting is April 18, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

**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. As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](http://example.com) and [PLLR Requirements for Prescribing Information](http://example.com) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- 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.

**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 information. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: [Reference ID: 4076446](http://example.com)).
Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient information, 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](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.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Oncology Products 1. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, contact Amy Tilley, Regulatory Project Manager, at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim, MD  
Director  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
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/

JULIA A BEAVER
03/29/2017
Signing on behalf of Dr. Kim
IND 117796
NDA 209935

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

ATTENTION: Concetta Freund, MS
Sr. Global Program Regulatory Manager

Dear Ms. Freund:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i)
of the Federal Food, Drug, and Cosmetic Act and to your New Drug Application (NDA) dated
and received January 30, 2017, submitted under section 505(b) of the Federal Food, Drug, and
Cosmetic Act for Ribociclib and Letrozole Tablets, 200 mg and 2.5 mg.

We also refer to your IND correspondence, dated and received December 22, 2016, and to your
NDA correspondence, dated and received January 30, 2017, requesting a review of your
proposed proprietary name, Kisqali Femara Co-Pack.

We have completed our review of the proposed proprietary name, Kisqali Femara Co-Pack and
have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your January 30, 2017, submission are
altered prior to approval of the marketing application, the proprietary name should be
resubmitted for review. Additionally, if your application receives a complete response, a new
request for name review for your proposed name should be submitted when you respond to the
application deficiencies.

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/Guid
  ances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through
  2017,
  (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM27
  0412.pdf)
If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application, contact Amy Tilley, Regulatory Project Manager in the Office of New Drugs at (301) 796-3994.

Sincerely,

{See appended electronic signature page}

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

/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
03/22/2017
Connie, the purpose of this email is to send you the attached FDA revised PI regarding NDA 209935 for Kisqali Femara Co-Pack. Please be sure to keep the PI in tracked changes and accept all revisions you agree with and delete all agreed to comments.

We request your emailed response no later than 10 am on Monday, March 27, 2017, and then follow up with an official response to the NDA.

Kindly confirm receipt of this email.

Regards.

Amy R. Tilley
Regulatory Project Manager
Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amy R Tilley
03/20/2017
Connie, the purpose of this email is to send you the FDA Carton and Container Label Revisions below regarding NDA 209935 for Kisqali Femara Co-Pack. We request your emailed response no later than 11 am on Monday, March 27, 2017, and then follow up with an official submission to the NDA. Kindly confirm receipt of this email.

A. Container label – Pull Out Blister Card for Kisqali 200 mg daily dose configuration
   1. The statement “(b)(4)” is inaccurate because there is no “(b)(4)” on the back of the blister card or blister card sleeve. Remove this statement to be consistent with the pull out blister card for Kisqali 400 mg daily dose and 600 daily dose.

B. Carton labeling – Kisqali Blister Card Sleeve
   1. To ensure patient’s understanding to take Kisqali for three weeks, followed by a one-week break, and to ensure patient uses the Dosing Calendar, relocate the dosing instructions that are currently on the back panel:

   Take (b)(4) once a day at (b)(4) the same time for three weeks, followed by a one-week break.

   Use the Dosing Calendar provided to keep track of your treatment as directed by your prescriber.

   Relocate these instructions to the front panel and merge them with the Usual Dosage statement, such that it reads:

   **Usual Dosage:** Take (b)(4) three] 200 mg tablets once a day at the same time for three weeks, followed by a one week break. Take with or without food. Swallow tablets whole. **DO NOT** chew, crush, or split tablets.

   Use the Dosing Calendar provided inside the box to keep track of your treatment as directed by your prescriber.

   This can be achieved by moving the storage information and the “Each tablet contains...” statements to the back panel.

C. Carton labeling for Kisqali Femara Co-Pack
   1. Since “Kisqali Femara Co-Pack” is the conditionally approved proprietary name for this product, revise the presentation of the proprietary name and established name so that the product name is presented as “Kisqali Femara Co-Pack (ribociclib and letrozole) tablets”. For example,
2. Remove the (b)(4) throughout the carton labeling.

3. Since Kisqali is only taken daily for three weeks, the Usual Dosage statement “Take three 200 mg Kisqali tablets (b)(4)
   once daily, with or without food. Swallow tablets whole.” on the back panel is inaccurate. Revise this statement to accurately reflect the correct
dosing regimen for Kisqali (i.e., once daily for 3 weeks followed by a one-
week break).

4. On the principal display panel, add the item “● Dosing Calendar” to bottom of the list under “This carton contains:”.

Regards,

Amy R. Tilley
Regulatory Project Manager
Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

Reference ID: 4071628
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

--------------------------------
AMY R TILLEY
03/17/2017
For CDER NDA/BLA reviews only: We are requesting that Division RPMs upload the PeRC PREA Template as a Memo To File into DARRTS in advance of your scheduled PeRC meeting.

Note: The PeRC’s recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. The final PeRC meeting minutes are linked to the NDA/BLA application in DARRTS.

Complete the section(s) of this template that are relevant to your current review. Sections that are not applicable can be deleted.

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.

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.
Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

**BACKGROUND**

Please check all that apply: ☒ Full Waiver ☐ Partial Waiver ☐ Pediatric Assessment ☐ Deferral/Pediatric Plan

**BLA/NDA#:** NDA 209935

**PRODUCT PROPRIETARY NAME:** Kisqali® Femara® CO-PACK  
**ESTABLISHED/GENERIC NAME:** Ribociclib and Letrozole

**APPLICANT/SPONSOR:** Novartis Pharmaceuticals Corporation

**PREVIOUSLY APPROVED INDICATION/S:**

(1) ______________________________________
(2) ______________________________________
(3) ______________________________________
(4) ______________________________________

**PROPOSED INDICATION/S:**

(1) KISQALI FEMARA CO-PACK, a co-packaged product containing ribociclib, a kinase inhibitor, and letrozole, an aromatase inhibitor, is indicated as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

(2) ______________________________________
(3) ______________________________________
(4) ______________________________________

**BLA/NDA STAMP DATE:** January 30, 2017

**PDUFA GOAL DATE:** November 30, 2017

**SUPPLEMENT TYPE:**
SUPPLEMENT NUMBER:

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 □

Are there any changes to the Agreed iPSP that are different than the sponsor’s current pediatric plan?  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. Birth to 18 years

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:

Studies are impossible or highly impractical (because, for example, the number of pediatric patients is so small or geographically dispersed)

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

Same as applicant

8 4 Pediatric Use

The safety and efficacy of KISQALI FEMARA CO-PACK in pediatric patients has 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
- acute bacterial exacerbations of chronic bronchitis
  (a complication of chronic obstructive pulmonary disease)
- adjunctive treatment of major depressive disorder
- age-related macular degeneration
- Alzheimer’s disease
- amyloidosis
- amyotrophic lateral sclerosis
- androgenic alopecia
- ankylosing spondylitis
- atherosclerotic cardiovascular disease
- benign monoclonal gammopathy
- benign prostatic hyperplasia
- cancer:
  - basal cell and squamous cell skin cancer
  - bladder
  - breast
  - cervical
  - colorectal
  - cholangiocarcinoma
  - endometrial
  - esophageal
  - fallopian tube
  - follicular lymphoma
  - gastric
  - hairy cell leukemia
  - hepatocellular
  - indolent non-Hodgkin lymphoma
  - liposarcoma
  - lung (small & non-small cell)
  - multiple myeloma
  - oropharynx (squamous cell)
  - ovarian (non-germ cell)
  - pancreatic
  - peritoneal
  - prostate
  - refractory advanced melanoma
  - renal cell
  - uterine
  - chronic lymphocytic leukemia
- chronic obstructive pulmonary disease
- cryoglobulinemia
- degenerative intervertebral disc disease
- diabetic peripheral neuropathy/macular edema
- diabetic foot infections
- diabetic retinopathy
- digestive disorders (gallstones)
- dry eye syndrome (keratoconjunctivitis sicca)
- dupuytren’s disease and manifestations
- erectile dysfunction essential thrombocytosis
- giant cell arteritis
- gout
- heavy menstrual bleeding associated with uterine fibroids
- Huntington’s chorea
- idiopathic pulmonary fibrosis
- infertility & reproductive technology
- juvenile psoriatic arthritis
- memory loss
- menopause and perimenopausal disorders
- mesothelioma
- microscopic polyangiitis
- myelodysplasia
- myelofibrosis & myeloproliferative disorders
- opioid induced constipation in chronic, non-cancer pain
- osteoarthritis
- overactive bladder
- Parkinson’s disease
- paroxysmal nocturnal hemoglobinuria
- plasma cells and antibody production disorders
- polycythemia vera
- polymyalgia rheumatica (PMR)
- 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
- retinal vein occlusions
- stress urinary incontinence
- Sjogren’s Syndrome
- temporary improvement in the appearance of caudal lines
- treatment of heavy uterine bleeding associated with uterine leiomyomata
- treatment of Hypoactive Sexual Desire Disorder (HSDD) in postmenopausal women
- 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:

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

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.)
   a. Adult studies are completed and ready for approval
   b. Additional safety or effectiveness data needed (describe)
   c. Other (specify)

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

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:
b. Study Completion:
c. Study Submission:

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:

Nonclinical Studies:

Clinical Studies:

Age group and population (indication) in which study will be performed:
This section should list the age group and population exactly as it is in the plan.

Example:
Study 1: patients aged X to Y years.
Study 2: sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.

Number of patients to be studied or power of study to be achieved:
Example:
Study 1: X subjects in each treatment arm and be powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% must be females and 25% must be less than 3 years.

Study 2: This study is powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters.

Entry criteria:
This section should list pertinent inclusion/exclusion criteria.

Example:
Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs
Patients must have a negative pregnancy test if female.

Clinical endpoints:

Example:
Study 1: Clinical outcome and safety will be the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG should attempt to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F.

Timing of assessments:

Example: baseline, week 1, 4, and 6
**Statistical information (statistical analyses of the data to be performed):**
*Example:*
Study 1 non-inferiority: two-sided 95% confidence interval (CI) of treatment difference in improvement rates should be within 25% of the control’s response rate.

Study 2: descriptive statistical methods for AUC, Cmax, Tmax, Cl/F and compared to adults.

**Division comments on product safety:**
Are there any safety concerns currently being assessed?  □ Yes  □ No

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:**

**Division comments on sponsor proposal to satisfy PREA:**
PeRC ASSESSMENT TEMPLATE

Please attach:

- [ ] Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.
- [ ] Pediatric Record

Date of PREA PMR:
Description of PREA PMR: *(Description from the PMC database is acceptable)*

Was Plan Reviewed by PeRC?  [ ] Yes  [ ] No  If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

**Indication(s) that were studied:**
This section should list the indication(s) exactly as written in the protocols.

*Example:*
*DRUG for the treatment of the signs and symptoms of disease x.*

**Number of Centers ____**

**Number and Names of Countries ____**

**Drug information:**

*Examples in italics*
- Route of administration: *Oral*
- *Formulation: disintegrating tablet*
- Dosage: 75 and 50 mg
- Regimen: list frequency of dosage administration
**Types of Studies/ Study Design:**

*Example:*

- **Study 1:** Multi-center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.
- **Study 2:** PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.

**Age group and population in which study/ies was/were performed:**

*Example:*

- **Study 1:** patients aged X to Y years.
- **Study 2:** sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.

**Number of patients studied or power of study achieved:**

*Example:*

- **Study 1:** X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.
- **Study 2:** powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients.

**Entry criteria:**

*This section should list pertinent inclusion/exclusion criteria.*

*Example:*

- **Entry criteria:** Pediatric patients with disease x diagnosed with laboratory test of LFTs
- **Patients had a negative pregnancy test if female.**

**Clinical endpoints:**
Example:
Study 1: Clinical outcome and safety were the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F

<table>
<thead>
<tr>
<th>Statistical information (statistical analyses of the data performed):</th>
</tr>
</thead>
<tbody>
<tr>
<td>This section should list the statistical tests conducted.</td>
</tr>
</tbody>
</table>

Example:
Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control’s response rate.

Study 2: descriptive statistical methods for AUC, Cmax, Tmax, CL/F and compared to adults.

<table>
<thead>
<tr>
<th>Timing of assessments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example:</td>
</tr>
<tr>
<td>Baseline, week 2, week 6, and end of treatment</td>
</tr>
<tr>
<td>Division comments and conclusions (Summary of Safety and Efficacy)</td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.</td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

______________________________________________
AMY R TILLEY
03/16/2017
Novartis Pharmaceuticals Corporation  
One Health Plaza Bldg.  
East Hanover, NJ 07936

ATTENTION: Concetta Freund, MS  
Sr. Global Program Regulatory Manager

Dear Ms. Freund:

Please refer to your New Drug Application (NDA) dated January 30, 2017, received January 30, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ribociclib and Letrozole Tablets, 200 mg (ribociclib); 2.5 mg (letrozole).

We acknowledge receipt of your January 30, 2017, correspondence, received January 30, 2017, requesting a review of your proposed proprietary name, Kisqali Femara CO-PACK.

If the application is filed, the user fee goal date will be April 30, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application, contact Amy Tilley, Regulatory Project Manager, in the Office of New Drugs at (301) 796-3994.

Sincerely,

{See appended electronic signature page}  

Wana Manitpisitkul, PharmD, BCPS  
Safety Regulatory Project Manager  
Office of Surveillance and Epidemiology  
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/

WANA MANITPISITKUL
03/03/2017
Dear Ms. Freund,

Reference is made to your NDA submitted on January 30, 2017. We also make reference to your request for Proprietary Name Review, to which we have the following information request regarding packaging:

For the proposed blister pack labels and carton labeling for Kisqali Femara Co-Pack (ribociclib and letrozole) NDA 209935, please submit representative samples of the Kisqali Femara Co-Pack including the Kisqali blister pack and Femara bottle with the dosing calendar packaged in the co-pack carton (one sample each for 200 mg daily dose, 400 mg daily dose, 600 mg daily dose) to aid in visualizing how the proposed product is packaged.

Please ship the samples to:

Frances Fahnbulleh, PharmD
10903 New Hampshire Avenue
Oak Building 22, 4th Fl. (Rm. 4404)
Silver Spring, MD 20993-0002

Please provide the samples by Monday, March 6, 2017.

Respectfully,

Frances Fahnbulleh

Frances Fahnbulleh, RPh, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
CDER/FDA/VO22, Rm#4404
Ph: 301-796-0942/Fax: 301-796-9832
Email: Frances.Fahnbulleh@fda.hhs.gov

THIS DOCUMENT IS INTENDED ONLY FOR USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error,
please notify us immediately by telephone at (301) 796-0942. Thank you.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FRANCES G FAHNBULEH
02/22/2017
Connie, my apologies as my previous email may be a bit confusing.

We need you to revise the co-pack label to reflect the updated ribociclib label.

I will call you to confirm your understanding of our request.

Regards.

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

Connie, it is my understanding the label for NDA 209902 for Ribociclib has had some agreed upon revisions. Please officially submit the Ribociclib label which contains the most current agreed to revisions to the Co-package NDA 209935 as soon as possible.

Please let me know the date you will be officially submitting this label so we can use that version to continue our review of the Co-Pack label.

Kindly confirm receipt of this email.

Regards.

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------------------------

AMY R TILLEY
02/22/2017
NDA 209935

NDA ACKNOWLEDGMENT

Novartis Pharmaceuticals Corporation
Attention: Concetta Freund
Sr. Global Program Regulatory Manager
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Freund:

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: Kisqali Femara Co-Pack (ribociclib and letrozole) Tablets 200 mg (ribociclib); 2.5 mg (letrozole)

Date of Application: January 30, 2017

Date of Receipt: January 30, 2017

Our Reference Number: NDA 209935

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 March 31, 2017, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR314.50(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).

Reference ID: 4059827
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 Oncology Products 1  
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 have any questions, contact me at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Amy R. Tilley  
Regulatory Project Manager  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
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/

----------------------------------------------------
AMY R TILLEY
02/22/2017
Connie, after conferring with my Chief, since there was no Clinical Data submitted with NDA 209935 and the Financial Disclosure information is referenced to NDA 209092 there is no need to submit anything else to the co-package NDA.

Thank you.

Amy

Hi Amy,

I wanted to follow up on my email yesterday. As mentioned, in NDA 209,935 we do have the cross-reference to NDA 209,092, along with the statement in the Notes-to-Reviewers, covering the financial disclosure information for the covered studies. However, if the Agency would like for us to update NDA 209,935 to have this information within the original application in Module 1.3.4, I am attaching the information, as requested. We can have this submitted via the Gateway by no later than Monday.

This is basically the same information submitted to the parent NDA 209,092, but updated with a statement saying since NDA 209,092 submission (August 29, 2016) to January 18, 2017, an assessment of any changes in financial interest for the clinical investigators involved in studies CLEE011A2301 and CLEE011X2107 was made. There is no change in financial interest from that submitted to NDA 209,092.

Please confirm receipt.

Thanks in advance,

Connie

Concetta Freund, MS
Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315
East Hanover, NJ 07936-1080
Office phone +1 862-778-3501
Cell phone + b (b)
connie.freund@novartis.com
Hi Amy,

Thank you. Please note that the FDFs for investigators were submitted in NDA 209,092, in conjunction with the covered studies and related data. A cross-reference was made to this info in NDA 209,935. In addition, Novartis assessed any changes in financial interest for the involved investigators since submission of NDA 209,092 through January 18th 2017, and no change in financial interest is made from what is on file in NDA 209,092. We included the following statement and information in NDA 209,935 “cover-notesreviewer”: “A statement regarding financial certification was submitted to NDA 209,092, and a cross-reference is made to this certification. Since NDA 209,092 submission (August 29, 2016) to January 18, 2017, an assessment of any changes in financial interest for the clinical investigators involved in studies CLEE011A2301 and CLEE011X2107 was made. There is no change in financial interest from that submitted to NDA 209,092 [NDA 209,092 financial-cert].

Please let me know if additional information is still required for NDA 209,935.

Kind regards,
Connie

---

Connetta Freund, MS
Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315
East Hanover, NJ 07936-1080
Office phone +1 862-778-3501
Cell phone [phononumber]
connie.freund@novartis.com
www.novartis.com

---

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Wednesday, February 08, 2017 11:13 AM
To: Freund, Connie <connie.freund@novartis.com>
Cc: Gao, Rose <rose.gao@novartis.com>
Subject: NDA 209935 Kisqali Femara Co-Pack - Financial Disclosure
Importance: High
Sensitivity: Confidential

Connie, the purpose of this email is to inquire whether or not the Financial Disclosure Form 3454 and/or 3455 were submitted with the original application. Upon my regulatory review of this submission, I am unable to locate the Financial Disclosure Form(s). If the form(s) were submitted in
the original application please let me know their location. If the forms were not submitted in the original application please do so immediately.

Kindly reply to this email as soon as possible and then follow up with an official submission to the NDA.

Regards.

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------------------------------
AMY R TILLEY
02/09/2017
Connie, the purpose of this email is to inquire whether or not the Financial Disclosure Form 3454 and/or 3455 were submitted with the original application. Upon my regulatory review of this submission, I am unable to locate the Financial Disclosure Form(s). If the form(s) were submitted in the original application please let me know their location. If the forms were not submitted in the original application please do so immediately.

Kindly reply to this email as soon as possible and then follow up with an official submission to the NDA.

Regards.

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY R TILLEY
02/08/2017
IND 117796

Novartis Pharmaceuticals Corporation
Attention: Concetta Freund, MS
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Ms. Freund:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ribociclib (LEE011).

We also refer to your submission dated September 22, 2016, containing a Type B meeting request. The purpose of the requested meeting was to gain agreement on the regulatory and administrative items related to the co-packaged NDA.

Further reference is made to our Meeting Granted letter dated October 7, 2016, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your October 20, 2016, background package.

If you have any questions, contact Tracy Cutler, Regulatory Health Project Manager at (301) 796-9608 or Tracy.Cutler@fda.hhs.gov.

Sincerely,

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

Tracy L. Cutler, MPH, CCRP, CIP
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Julia Beaver, MD
Associate Division Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Written Responses
Meeting Type: Type B  
Meeting Category: Pre-NDA  
Application Number: IND 117796  
Product Name: Ribociclib (LEE011)  
Indication: Breast cancer  
Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation  
Regulatory Pathway: 505(b)(1)  

1.0 BACKGROUND

Novartis has requested a Type B Pre-NDA Meeting with FDA to a) discuss and gain agreement on the co-package NDA content and format, as well as the overall submission strategy as it relates to co-packaged products (ribociclib and letrozole) and cross referencing their respective “parent” NDAs and b) gain agreement on regulatory and administrative items related to this co-package NDA.

The initial registration strategy for ribociclib involves targeting advanced hormone receptor positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative breast cancer in the first line setting in combination with letrozole [Study CLEE011A2301 (MONALEESA-2)]. Pivotal data from study CLEE011A2301 was the subject of a Type B (Pre-NDA) meeting held on July 21, 2016, and serves as the pivotal registration study for NDA 209092 (submitted August 29, 2016, under review). The clinical efficacy and safety data submitted in NDA 209092, along with information submitted in Femara NDA 20726, will also serve as the registrational basis for this proposed co-package NDA.

The proposed indication for ribociclib co-packaged with letrozole is:

“[Tradename Y], (ribociclib 

\[4\]) letrozole is indicated for treatment of postmenopausal women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer”.

This is similar to the indication currently under evaluation in ribociclib’s submitted NDA 209092:

“[Tradename X], (b) (4) is indicated in combination with \(\text{(d)(4)}\) for the treatment of postmenopausal women with hormone receptor (HR)- positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer”.
The Center for Drug Evaluation and Research (CDER), Division of Oncology Products 1 (DOP1) is currently reviewing NDA 209092 [the Day 60 filing target is October 28, 2016, in accordance with 21 CFR 314.101(a), and as confirmed in the September 7, 2016, NDA acknowledgment letter]. Novartis is planning to submit an additional New Drug Application (NDA) to support the registration of ribociclib co-packaged with letrozole (Femara®), hereafter referred to as the “co-pack” for convenience within this document.

This “co-pack” will contain the individual drug products of ribociclib and letrozole. The 28-day cycle dosing regimen (ribociclib: 3 weeks on/1 week off vs continuous 28-day dosing for letrozole) is summarized in NDA 209092. Ribociclib will be provided as 200 mg tablets in blister packs for 21-day dosing, as described in NDA 209092 (600 or 400 mg dose) and letrozole will be provided in the commercial form of 2.5 mg tablets (28-tablet count bottle for 28-day dosing).

Proposed Tradename Y “co-packs”:
- Ribociclib 600 mg (3 x 200 mg) for 21 days (63 tablets) + letrozole 2.5 mg (1 x 2.5 mg) for 28 days (28 tablets)
- Ribociclib 400 mg (2 x 200 mg) for 21 days (42 tablets) + letrozole 2.5 mg (1 x 2.5 mg) for 28 days (28 tablets)

2.0 QUESTIONS AND RESPONSES

**Question 1**: In accordance with the published proposed rules on co-packaged products and fixed-drug combinations (Federal Register / Vol. 80, No. 246; Dec 23, 2015), and the Food and Drug Administration’s (FDA) 2013 Guidance for Industry: Codevelopment of Two or More New Investigational Drugs for Use in Combination”, Novartis is planning for the submission of a single NDA for co-packaged products [ribociclib co-packaged with Femara® (letrozole), “copack” NDA].

Does the Agency concur with the planned submission of a “co-pack” NDA?

**FDA Response**: Yes.

**Question 2**: The proposed United States Prescribing Information (US PI) will be a single, integrated label covering the “co-pack”, in accordance to the 2013 Guidance for Industry “Codevelopment of Two or More New Investigational Drugs for Use in Combination”.

Does the Agency agree with this general plan for a single proposed US PI for the co-packaged product?

**FDA Response**: Yes.
**Question 3:** A Clinical Overview (CO) will be submitted as the primary summary for the “co-pack” NDA. The only additional Module 2 documents currently planned for submission in the “co-pack” NDA include 2.2 Introduction and 2.3 Quality Overall Summary (QoS). Please refer to Question 4 and accompanying position. The CO will highlight any potential areas of importance from the perspective of the co-packaged products in combination, and as individual drugs. A focus of the CO will be on the description of ribociclib and letrozole information not specifically cross-referenced.

Does the Agency agree with this approach to the Clinical Overview?

**FDA Response:** Yes.

**Question 4:** For this “co-pack” NDA, Novartis is planning to submit cross-references to key relevant components of the ribociclib NDA (209,092) submission, and the approved Femara® NDA (20726).

Does the Agency agree with this cross-referencing approach?

**FDA Response:** Yes.

**Question 5:** For drug product information, does the Agency agree with the cross-reference submission plan outlined below to support the co-pack NDA submission?

**FDA Response:** Yes.

**Question 6:** Novartis is of the opinion that the “co-pack” NDA can be submitted during the review of the NDA 209092 (at a point after the Agency provides the “co-pack” pre-NDA meeting written responses) with the accompanying cross-references made to NDA 209092, as previously outlined, as there is no new efficacy and safety data planned for this “co-pack” NDA.

Does the Agency agree with this approach?

**FDA Response:** Yes.

**Question 7:** Breakthrough Therapy designation was granted for the combination of ribociclib plus letrozole as “initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer”.

Novartis would like to clarify if the features and provisions of Breakthrough Therapy Designation are also applicable and can be extended to the planned co-packaged NDA?

**FDA Response:** The Breakthrough Therapy designation is granted for the drug (or drug combination) and the indication. As the proposed drug combination and indication are the same for the proposed marketing application as they are for the granted Breakthrough
Therapy designation, the “co-pack” NDA should be reviewed as a Breakthrough Therapy program application.

**Question 8:** A proprietary name proposal for the “co-pack” (Tradename Y for the co-packaged products) will be submitted to IND 117796 for conditional approval as per standard processes. Does the Agency agree that, if the proposed proprietary name conditional approval is pending under IND 117796, Novartis will submit updates (if any) at the time of NDA submission and cross-reference to the proprietary name review request submitted to IND 117796?

**FDA Response:** A Request for Proprietary Name Review for the “co-pack” product must be submitted with the “co-pack” NDA when the “co-pack” NDA is submitted. You may cross-reference the Request for Proprietary Name Review for the “co-pack” submitted to IND 117796 and provide the label and labeling for the “co-pack” to the NDA submission.

**Question 9:** Does the Agency agree that the “co-pack” NDA may qualify for a reduction in the User Fee amount, to be determined at the time of the User Fee reduction submission request?

**FDA Response:** The “co-pack” NDA may qualify for a reduced application user fee provided that the following are true:

1. The clinical data required to support the approval of the “co-pack” NDA were previously reviewed under user-fee paying applications/supplements;

   AND

2. The clinical data does not require a re-review or re-analysis to support approval of the “co-pack” NDA.

As both NDA 209092 and NDA 020726 paid an application user fee, if the clinical data submitted therein will be the only clinical data used to support the approval of the new “co-pack” NDA, and the review division does not anticipate that re-analysis of that clinical data will be necessary, then the “co-pack” NDA may qualify for a reduced application user fee. Please note the final determination regarding user fees will occur when the application is submitted in its entirety to the Agency.

**Question 10:** Does the Agency agree that the review timelines outlined in Appendix A of the Center for Drug Evaluation and Research’s (CDER) “21st Century Review Process Desk Reference Guide (DRG)” will apply for the co-pack NDA (i.e. a review period no longer than 10-months maximum)?

**FDA Response:** As NDA 209092 ribociclib (a new molecular entity) is still pending and is not approved at this time, a “co-pack” NDA submission containing ribociclib would also fall under PDUFA V’s “Program”. The PDUFA time clock will begin 60 days after application receipt and the application is filed, with a maximum review period no longer
than 10 months. A determination of standard versus priority review of the “co-pack” NDA submission will be made during the filing review period.

3.0 OTHER IMPORTANT MEETING LANGUAGE

3.1 Discussion of the Content of a Complete Application

As stated in our October 7, 2016, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

3.2 PREA Requirements

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 (iPSP) 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. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

3.3 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 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- 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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

3.4 Manufacturing Facilities

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.
Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Federal Establishment Indicator (FEI) or Registration Number (CFN)</th>
<th>Drug Master File Number (if applicable)</th>
<th>Manufacturing Step(s) or Type of Testing [Establishment function]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Corresponding names and titles of onsite contact:

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Onsite Contact (Person, Title)</th>
<th>Phone and Fax number</th>
<th>Email address</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.5 **Office of Scientific Investigations (OSI) Requests**

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).

1. **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.”

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item¹</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>I</td>
<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Line listings, by site)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files
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.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov
CDER Breakthrough Therapy Designation Determination Review Template

<table>
<thead>
<tr>
<th>IND/NDA/BLA #</th>
<th>IND 117796</th>
</tr>
</thead>
<tbody>
<tr>
<td>Request Receipt Date</td>
<td>6/3/2016</td>
</tr>
<tr>
<td>Product</td>
<td>Ribociclib (LEE011)</td>
</tr>
<tr>
<td>Indication</td>
<td>Advanced Breast Cancer</td>
</tr>
<tr>
<td>Drug Class/Mechanism of Action</td>
<td>Cyclin-dependent kinase inhibitor</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Novartis Pharmaceuticals</td>
</tr>
<tr>
<td>ODE/Division</td>
<td>Division of Oncology Products 1 (DOP1)</td>
</tr>
<tr>
<td>Breakthrough Therapy Request Goal Date (within 60 days of receipt)</td>
<td>8/2/2016</td>
</tr>
<tr>
<td>Review Date</td>
<td>06/30/2016</td>
</tr>
</tbody>
</table>

Note: This document should be uploaded into CDER’s electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

Ribociclib in combination with letrozole is indicated as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer.

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?  
   ☒YES ☐NO

3. Consideration of Breakthrough Therapy Criteria:
   a. Is the condition serious/life-threatening1)?  
      ☒YES ☐NO

   If checked “Yes”, proceed with below:
   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
      ☒YES the BTDR is adequate and sufficiently complete to permit a substantive review
      ☐Undetermined
      ☐NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):
      i. Only animal/nonclinical data submitted as evidence
      ☐
      ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
         ☐

iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g., multiple sclerosis, depression) □

iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) □

v. No or minimal clinically meaningful improvement as compared to available therapy\(^2\) historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) □

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation □

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Breast cancer is the most common cancer in women and the second most common cause of cancer death. SEER estimates that 40,450 women in the United States will die of breast cancer in 2016. Breast cancer is commonly subdivided into a small number of molecular subtypes based upon expression of the estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor. The most prevalent subtype is ER and/or PR positive, HER2 negative breast cancer, which comprises about 60% of new cases each year, and is even more common in postmenopausal women, the demographic group at greatest risk of developing the disease.

Ribociclib is an inhibitor of cyclin-dependent kinases (CDK) 4 and 6, which are involved in cell signaling pathways that culminate in cell cycle progression and cellular proliferation. Ribociclib inhibits tumor growth in a dose-dependent fashion in human cancer xenograft models, and the combination of ribociclib plus antiestrogens results in superior inhibition of tumor growth versus either class of agents given as monotherapy.

Another CDK inhibitor, palbociclib, was previously granted breakthrough designation and is currently available under accelerated approval in combination with the same backbone endocrine therapy partner (the aromatase

inhibitor, letrozole) for the same first-line hormone receptor-positive, HER2-negative metastatic breast cancer indication being sought in the current request. (See response to Q9 for further details.)

7. **Information related to endpoints used in the available clinical data:**

The endpoints that have been accepted by DOP1 and OHOP as clinically significant for patients with metastatic ER/PR positive, HER2 negative breast cancer, have been overall survival (OS) and progression-free survival (PFS) if the magnitude is sufficiently large as to be clinically meaningful, with a favorable benefit/risk ratio. The primary endpoint of the trial that serves as the basis of the current breakthrough designation request (MONALEESA-2) is progression-free survival (PFS). Progression-free survival improvements of similar magnitude have served as the basis for regular approval in first-line treatment for hormone receptor-positive, HER2-negative metastatic breast cancer.

8. **A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:**

There are numerous available therapies under regular approval specifically for first-line treatment of metastatic hormone receptor-positive, HER2-negative breast cancer, including the selective estrogen receptor modulator (SERM), tamoxifen; non-steroidal aromatase inhibitors, letrozole and anastrozole; and steroidal aromatase inhibitor, exemestane.

The following table taken from the FDA clinical review of palbociclib shows the therapies available under regular approval for the proposed first-line ER positive advanced breast cancer population.

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Relevant Indication</th>
<th>Year of Approval</th>
<th>Dosing/ Administration</th>
<th>Basis for approval</th>
<th>Important Safety and Tolerability Issues</th>
<th>Drug Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole</td>
<td>First and second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer</td>
<td>1997</td>
<td>2.5mg daily by mouth</td>
<td>Vs. tamoxifen TTP: 9.4 months vs. 6.0 months HR 0.72 (p&lt;0.0001) OS: 35 months vs. 32 months (P=0.0136)</td>
<td>Bone mineral density decrease, hot flashes, and arthralgias</td>
<td>Aromatase inhibitor</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>First-line treatment of postmenopausal women with HR-positive or unknown locally advanced or metastatic breast cancer</td>
<td>1995</td>
<td>1mg daily by mouth</td>
<td>Vs. tamoxifen TTP: 11.1 months vs. 5.8 months (p=0.006) and 8.2 vs 8.3 months (p=0.92)</td>
<td>Bone mineral density decrease, hot flashes, and arthralgias</td>
<td>Aromatase inhibitor</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>In the treatment of metastatic breast cancer in women and men. Patients whose tumors are estrogen receptor positive are more likely to benefit.</td>
<td>1977</td>
<td>20mg daily by mouth</td>
<td>Response rate in 14 Phase 2 studies and nine literature reports. The overall database included 1164 patients</td>
<td>Uterine malignancies, stroke, pulmonary embolism and hot flashes</td>
<td>Selective estrogen receptor modulator</td>
</tr>
<tr>
<td>Exemestane</td>
<td>Treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy</td>
<td>1999</td>
<td>25mg daily by mouth</td>
<td>Vs. megestrol TTP: 20.3 weeks vs. 15.6 weeks (HR 0.84)</td>
<td>Bone mineral density decrease, hot flashes, and arthralgias</td>
<td>Aromatase inhibitor</td>
</tr>
</tbody>
</table>

TTP: Time to Tumor Progression; OS: Overall Survival
In addition, another CDK inhibitor, palbociclib, is currently available under accelerated approval in combination with the same backbone endocrine therapy partner (letrozole) for the same first-line hormone receptor-positive, HER2-negative metastatic breast cancer indication being sought in the current request. (See related response to Q9 below.)

Numerous single agent cytotoxic agents (e.g. paclitaxel, capecitabine, and others) also constitute available therapy and may be used in selected first-line patients with rapidly progressive metastatic hormone receptor positive, HER2-negative breast cancer or extensive visceral involvement.

The current standard of care for treatment of advanced hormone receptor-positive, HER2-negative breast cancer is to exhaust endocrine therapy, alone or in combination with targeted therapy, due to the more favorable toxicity profile of these agents relative to cytotoxic therapy.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation.

As of June 2016, two other agents being studied for advanced hormone receptor positive, HER2-negative breast cancer have been granted breakthrough therapy designation based on data in similar patient populations (patients with advanced hormone receptor positive, HER2-negative breast cancer and minimal or no prior endocrine therapy for metastatic disease):

1. PD 0332991 (palbociclib/Ibrance®) IND #, BTD granted 04/09/2013

Another CDK inhibitor, palbociclib (Ibrance®), was granted breakthrough therapy designation in combination with the same backbone endocrine therapy partner (letrozole) for the same first-line hormone receptor-positive, HER2-negative metastatic breast cancer indication being sought in this request. A randomized phase 2 trial (PALOMA-1) of the aromatase inhibitor, letrozole, with or without palbociclib in 165 patients with first-line advanced ER positive, HER2 negative breast cancer demonstrated at the time of an interim analysis an improvement in median PFS (HR 0.37, p < 0.001) for the combination and resulted in granting of breakthrough designation. Final results from the same trial demonstrated a 10 month prolongation in median PFS (HR 0.49, p = 0.0004) for the combination, with a favorable trend in response rate (55% vs. 39%), duration of response (20.3 mos vs. 11.1 mos), clinical benefit rate (81% vs. 58%), and median OS (37.5 mos vs. 33.3 mos). These data from the PALOMA-1 trial also served as the basis for accelerated approval for treatment of first-line hormone receptor-positive, HER2-negative metastatic breast cancer in combination with letrozole.

In addition, palbociclib was granted regular approval in combination with fulvestrant for patients with hormone receptor-positive, HER2-negative metastatic breast cancer who have received prior endocrine therapy based upon a positive randomized phase 3 trial (PALOMA-3).

2. MS-275 (entinostat) IND, BTD granted 09/05/2013

Entinostat is a histone deacetylase (HDAC) inhibitor from Syndax Pharmaceuticals. Entinostat was granted breakthrough therapy designation based upon results of a randomized phase 2 trial (ENCORE 301).
10. Information related to the preliminary clinical evidence:

The breakthrough request is based upon the results of a single randomized, placebo-controlled phase 3 trial, CLEE011A2301 (MONALEESA-2). This trial enrolled 668 postmenopausal women with previously untreated advanced hormone receptor positive, HER2 negative breast cancer and randomized them to receive letrozole 2.5 mg/day in combination with either ribociclib 600 mg/day (3 weeks on/1 week off) or placebo. The primary endpoint was progression-free survival (PFS) as assessed by local investigator. Key secondary endpoints included overall survival (OS) and objective response rate (ORR). The study met its primary endpoint, demonstrating a superior PFS for the combination with a hazard ratio of 0.56 (95% CI 0.43, 0.72), p < 0.001. The median PFS duration was not reached for the investigational arm (95% CI 19.3, NE) months versus 14.7 months (95% CI 13.0, 16.5) for the control arm. Of potential concern, a blinded independent central review had a very high level of censored events, but yielded similar top-line results with a HR of 0.59 (95% CI 0.41, 0.85), p=0.002. At the time of the first OS analyses, only 43 events had been observed (11% of total 400 anticipated), and thus data were not yet mature, however there were 23 deaths (6.9%) in the investigational arm and 19 deaths (5.8%) in the control arm. The majority of deaths were due to breast cancer. There was 1 sudden death in the investigational arm versus 0 in the control arm and 1 death of unknown cause in the investigational arm versus 0 in the control arm. The overall response rate was higher in the investigational arm at 41% (95% CI 35, 46) than in the control arm at 28% (95% CI 22, 32) by local investigator assessment. The difference in response rates was due to a difference in partial responses. There were a total of 9 complete responses in the investigational arm versus 7 in the control arm.

Adverse events of all grades occurred in virtually all patients on both arms (99% vs. 97%). Grade 3 adverse events (66% vs. 32%) and grade 4 adverse events (15% vs. 1%) were much more common in the investigational arm compared with the control arm. Discontinuations due to adverse event (15% vs. 3%) and dose interruptions/reductions (73% vs. 16%) were also more common in the investigational arm. The most common adverse events in patients receiving letrozole plus ribociclib were neutropenia (61% vs. 4%), nausea (52% vs. 29%), fatigue (37% vs. 30%), and diarrhea (25% vs. 22%). Adverse events of special concern identified with ribociclib include QT prolongation and hepatotoxicity. A post-baseline QTcF of >480 ms occurred in 11 patients (3.3%) of patients in the ribociclib arm (of whom 9 out of 11 continued treatment without interruption and 2 continued treatment after a two week dose delay) versus 1 (0.3%) patient in the control arm. A >60 ms increase in baseline in QTcF was observed in 2.7% of patients in the ribociclib arm versus 0% of patients in the control arm. Grade 3/4 elevations in AST and ALT occurred in 7% and 10% versus 2% and 1% of subjects on the ribociclib arm versus the control arm, respectively. There were 4 patients (1.2%) on the ribociclib arm versus 1 patient (0.3%) on the control arm who meet the definition of Hy’s Law.

11. Division’s recommendation and rationale (pre-MPC review):

☒ GRANT:

The observed magnitude of improvement in PFS with addition of ribociclib to letrozole is clinically meaningful and comparable to that achieved with palbociclib. Ribociclib represents a substantial improvement over available therapy in view of the fact that palbociclib, another CDK inhibitor for the same indication, is still under accelerated approval.

☐ DENY:
12. Division’s next steps and sponsor’s plan for future development:

The Division would advise the Sponsor regarding conduct of ongoing phase 3 trials, as well as assist with manufacturing considerations under a compressed timeline for drug approval.

13. List references, if any:

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 1/15/16/M. Raggio
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TANYA M PROWELL
08/01/2016

JULIA A BEAVER
08/01/2016

GEOFFREY S KIM
08/02/2016
Dear Ms. Shen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ribociclib (LEE011).

We also refer to your June 3, 2016, request for Breakthrough Therapy designation. We have reviewed your request and have determined that ribociclib (LEE011), in combination with letrozole, as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of ribociclib (LEE011), in combination with letrozole, as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.¹

When Breakthrough Therapy designation is granted, sponsors are asked to submit a Type B meeting request for a multidisciplinary comprehensive discussion of the drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - Good Review Practice: Management of


Reference ID: 3966817
Breakthrough Therapy-Designated Drugs and Biologics, Attachment 1, for potential topics for discussion at this initial Breakthrough Therapy meeting.

We note your recent Pre-NDA meeting held on July 21, 2016. At this point in your drug development program, holding this initial Breakthrough Therapy meeting is not necessary. However, please contact the Regulatory Project Manager noted below to determine if any information is required at this time to expedite the review of your breakthrough designated product.

If the Breakthrough Therapy designation for ribociclib (LEE011), in combination with letrozole, as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Tracy Cutler, Regulatory Health Project Manager, at (301) 796-9608.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

---

2 http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEOFFREY S KIM
08/02/2016