

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205598Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

# ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION <sup>1</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NDA # 205598                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | NDA Supplement #<br>BLA Supplement # | If NDA, Efficacy Supplement Type:<br><i>(an action package is not required for SE8 or SE9 supplements)</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Proprietary Name: Macrilen<br>Established/Proper Name: macimorelin acetate<br>Dosage Form: oral solution                                                                                                                                                                                                                                                                                                                                                                                       |                                      | Applicant: Aeterna Zentaris GmbH<br>Agent for Applicant (if applicable): Aeterna Zentaris, Inc.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| RPM: Meghna M. Jairath, Pharm.D.                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                      | Division: Metabolism & Endocrinology Products                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)<br>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)<br><br>BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)<br>Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)                                                                                                      |                                      | <b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b> <div style="margin-left: 20px;"> <input type="checkbox"/> No changes<br/> <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i><br/>           Date of check:         </div> </li> </ul> <p><i><b>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.</b></i></p> |
| ❖ Actions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>December 30, 2017</u> but action was taken on <u>December 20, 2017</u></li> </ul>                                                                                                                                                                                                                                                                                                                     |                                      | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>                                                                                                                                                                                                                                                                                                                                                                        |                                      | CR- 11/5/14                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?<br>Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____ |                                      | <input type="checkbox"/> Received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| ❖ Application Characteristics <sup>3</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

<sup>1</sup> 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.

<sup>2</sup> 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).

<sup>3</sup> 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 ☐ Priority  
Chemical classification (new NDAs only):  
(confirm chemical classification at time of approval)

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

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

BLAs: Subpart E

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

Subpart H

- ☐ Approval based on animal studies

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

Comments:

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

| Action Letters                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ❖ Copies of all action letters <i>(including approval letter with final labeling)</i>                                                                                                     | Action(s) and date(s)<br>AP- 12/20/17<br>CR-11/5/14                                                                                                                                                                                                                                                                           |
| Labeling                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                               |
| ❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>                                                                                          |                                                                                                                                                                                                                                                                                                                               |
| • Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>                                                                           | <input checked="" type="checkbox"/> Included                                                                                                                                                                                                                                                                                  |
| • Original applicant-proposed labeling                                                                                                                                                    | <input checked="" type="checkbox"/> Included                                                                                                                                                                                                                                                                                  |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>                    | <input type="checkbox"/> Medication Guide<br><input type="checkbox"/> Patient Package Insert<br><input type="checkbox"/> Instructions for Use<br><input type="checkbox"/> Device Labeling<br><input checked="" type="checkbox"/> None                                                                                         |
| • Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>                                                                           | <input type="checkbox"/> Included                                                                                                                                                                                                                                                                                             |
| • Original applicant-proposed labeling                                                                                                                                                    | <input type="checkbox"/> Included                                                                                                                                                                                                                                                                                             |
| ❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>                          |                                                                                                                                                                                                                                                                                                                               |
| • Most-recent draft labeling                                                                                                                                                              | <input checked="" type="checkbox"/> Included                                                                                                                                                                                                                                                                                  |
| ❖ Proprietary Name <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>• Review(s) <i>(indicate date(s))</i></li> </ul> | Acceptable: 11/15/17<br>Review: 11/14/17<br><br>Non-acceptable: 9/25/17<br>Review: 9/22/17<br><br>Acceptable: 1/27/14<br>Review: 1/16/14                                                                                                                                                                                      |
| ❖ Labeling reviews <i>(indicate dates of reviews)</i>                                                                                                                                     | RPM: 1/15/14<br>DMEPA: 12/15/17; 11/20/17;<br>8/11/14; 8/5/14; 5/16/14; 2/26/14<br>DMPP/PLT (DRISK): none<br>OPDP: 12/18/17;10/24/14<br>SEALD: <input checked="" type="checkbox"/> None<br>CSS: <input checked="" type="checkbox"/> None<br>Product Quality <input checked="" type="checkbox"/> None<br>Other: DPMH- 12/11/17 |
| Administrative / Regulatory Documents                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                               |
| ❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>                                                                                            | 1/15/14                                                                                                                                                                                                                                                                                                                       |
| ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee                                                                                                    | <input checked="" type="checkbox"/> Not a (b)(2)                                                                                                                                                                                                                                                                              |
| ❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>                                                                                                     | <input checked="" type="checkbox"/> Completed (Do not include)                                                                                                                                                                                                                                                                |

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

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| ❖ Application Integrity Policy (AIP) Status and Related Documents<br><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>                                                                                                                                                                                                                                |                                                                                                                      |
| <ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                               | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No                                                  |
| <ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>                                                                                                                                                                             | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No<br><br><input type="checkbox"/> Not an AP action |
| ❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC _____<br/>If PeRC review not necessary, explain: _____</li> </ul>                                                                                                                                                                                                                                                                                                                   | Did not go to PeRC because of orphan designation                                                                     |
| ❖ Breakthrough Therapy Designation                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <input checked="" type="checkbox"/> N/A                                                                              |
| <ul style="list-style-type: none"> <li>Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                      |
| <ul style="list-style-type: none"> <li>CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>                                                                                                                                                                                                                                                             |                                                                                                                      |
| <ul style="list-style-type: none"> <li>CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a>)</p>                                                                                                               |                                                                                                                      |
| ❖ 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.) ( <i>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</i> ) | <b>included</b>                                                                                                      |
| ❖ 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                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                      |
| <ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>                                                                                                                                                                                                                                                                                                                                                | <input checked="" type="checkbox"/> N/A or no mtg                                                                    |
| <ul style="list-style-type: none"> <li>Pre-NDA/BLA or BPD Type 4 meeting (<i>indicate date of mtg</i>)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                       | <input checked="" type="checkbox"/> No mtg                                                                           |
| <ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                            | <input checked="" type="checkbox"/> No mtg                                                                           |
| <ul style="list-style-type: none"> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                 | 4/24/14 (minutes); 4/16/14 (date)                                                                                    |
| <ul style="list-style-type: none"> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                      | 8/14/14 (minutes); 7/23/14 (background package); 7/14/14 (date)                                                      |
| <ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, BPD Type 3, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>                                                                                                                                                                                                                                                                                                                    | n/a                                                                                                                  |

|                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| ❖ Advisory Committee Meeting(s)                                                                                                                                                                                                                                                                                                                                                                                       | <input checked="" type="checkbox"/> No AC meeting      |
| • Date(s) of Meeting(s)                                                                                                                                                                                                                                                                                                                                                                                               |                                                        |
| <b>Decisional and Summary Memos</b>                                                                                                                                                                                                                                                                                                                                                                                   |                                                        |
| ❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                            | 11/5/2014                                              |
| Division Director Summary Review ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                             | 12/5/17; 11/5/2014                                     |
| Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                          | 10/31/2014                                             |
| PMR/PMC Development Templates ( <i>indicate total number</i> )                                                                                                                                                                                                                                                                                                                                                        | <input checked="" type="checkbox"/> None               |
| <b>Clinical</b>                                                                                                                                                                                                                                                                                                                                                                                                       |                                                        |
| ❖ Clinical Reviews                                                                                                                                                                                                                                                                                                                                                                                                    |                                                        |
| • Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                             | <input checked="" type="checkbox"/> No separate review |
| • Clinical review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                                         | 11/24/17; 9/9/2014; 12/20/2013                         |
| • Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                   | <input checked="" type="checkbox"/> None               |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )                                                                                                                                              | Page 14 of 11/24/17 clinical review                    |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> ) <sup>5</sup>                                                                                                                                                                                                                                                                                    | IRT/QT-11/22/17                                        |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )                                                                                                                                                                                                                                                                                                          | <input checked="" type="checkbox"/> N/A                |
| ❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul> | 11/27/17; 7/3/14                                       |
| ❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )                                                                                                                                                                                                                                                                                                               | 11/21/17; 9/9/14                                       |
| <b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None                                                                                                                                                                                                                                                                                                                                                 |                                                        |
| ❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                | <input type="checkbox"/> No separate review            |
| Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/> None                          |
| <b>Biostatistics</b> <input type="checkbox"/> None                                                                                                                                                                                                                                                                                                                                                                    |                                                        |
| ❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                    | <input checked="" type="checkbox"/> No separate review |
| Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                            | <input checked="" type="checkbox"/> No separate review |
| Statistical Review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                                        | 11/30/17; 7/9/14; 12/31/13                             |

<sup>5</sup> 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).

| Clinical Pharmacology <input type="checkbox"/> None                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| ❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                  | <input checked="" type="checkbox"/> No separate review                                                                                        |
| Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                          | <input checked="" type="checkbox"/> No separate review                                                                                        |
| Clinical Pharmacology review(s) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                                      | 11/22/17; 10/3/14; 8/7/2014; 7/16/2014; 12/9/2013                                                                                             |
| ❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>                                                                                                                                                                                                                                                                                                                                | <input checked="" type="checkbox"/> None requested                                                                                            |
| Nonclinical <input type="checkbox"/> None                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                               |
| ❖ Pharmacology/Toxicology Discipline Reviews                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                               |
| • ADP/T Review(s) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                                                    | 10/31/2014 (2)                                                                                                                                |
| • Supervisory Review(s) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                                              | <input checked="" type="checkbox"/> No separate review                                                                                        |
| • Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                              | 10/24/17; 6/5/2014; 12/6/2013                                                                                                                 |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                         | <input checked="" type="checkbox"/> None                                                                                                      |
| ❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                   | <input checked="" type="checkbox"/> No carc                                                                                                   |
| ❖ ECAC/CAC report/memo of meeting                                                                                                                                                                                                                                                                                                                                                                                           | <input checked="" type="checkbox"/> None<br>Included in P/T review, page                                                                      |
| ❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>                                                                                                                                                                                                                                                                                                                                          | <input checked="" type="checkbox"/> None requested                                                                                            |
| Product Quality <input type="checkbox"/> None                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                               |
| ❖ Product Quality Discipline Reviews <sup>6</sup>                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                               |
| • Tertiary review <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                                                    | <input checked="" type="checkbox"/> None                                                                                                      |
| • Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                              | <input checked="" type="checkbox"/> None                                                                                                      |
| • Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                 | 11/17/17; 9/15/14; 7/3/2014; 12/19/13;                                                                                                        |
| ❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>                                                                                                                                                                                                                                                                                             | Biopharm: 6/17/14<br>Microbiology: 11/6/13                                                                                                    |
| ❖ Environmental Assessment (check one) (original and supplemental applications)                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                               |
| <input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>                                                                                                                                                                                                                                  | 11/17/17; pg 80                                                                                                                               |
| <input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                               |
| <input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>                                                                                                                                                                                                                                                                                                                      |                                                                                                                                               |
| ❖ Facilities Review/Inspection                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                               |
| <input checked="" type="checkbox"/> Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation <b>before issuing approval letter</b> ) <i>(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> | <input checked="" type="checkbox"/> Acceptable<br><input type="checkbox"/> Withhold recommendation<br><input type="checkbox"/> Not applicable |

<sup>6</sup> 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                                                                                                                                                                                                        |                                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>                                             | n/a<br>New patent/exclusivity ( <i>Notify CDER OND IO</i> )<br>n/a |
| <ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>                                                                                                                                                 | n/a                                                                |
| ❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>                                                                                          | n/a<br>( <i>Send email to CDER OND IO</i> )                        |
| ❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul> | n/a                                                                |
| ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email                                                                                                                                 | <input checked="" type="checkbox"/> Done                           |
| ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter                                                                            | <input checked="" type="checkbox"/> Done                           |
| ❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name                            | <input checked="" type="checkbox"/> Done                           |
| ❖ Ensure Pediatric Record is accurate                                                                                                                                                                                             | n/a                                                                |
| ❖ Send approval email within one business day to CDER-APPROVALS                                                                                                                                                                   | X                                                                  |
| ❖ Take Action Package (if in paper) down to Document Room for scanning within <b>two business days</b>                                                                                                                            | X                                                                  |

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/s/  
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MEGHNA M JAIRATH  
12/20/2017

**From:** [Jairath, Meghna](#)  
**To:** ["Mueller, Gilbert"](#)  
**Subject:** Final FDA PI NDA 205598  
**Date:** Monday, December 18, 2017 4:52:32 PM  
**Attachments:** [FDA final PI NDA 205598 12 18 17.doc](#)  
**Importance:** High

---

Hello,

I am sending you the final drat to the PI. This is our final draft version since we expect no further negotiations. Please clean up the label and send back us to by **December 19, 2017**.

Do no submit anything to the NDA until we have finalized the labeling.

Also, we will be taking an early action on the this.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
12/18/2017

**From:** [Jairath, Meghna](#)  
**To:** [Mueller, Gilbert](#)  
**Subject:** Round 2 PI NDA 205598  
**Date:** Wednesday, December 06, 2017 1:25:12 PM  
**Attachments:** [FDA round 2 PI NDA 205598 PI\\_12\\_6\\_2017 \(002\).doc](#)  
**Importance:** High

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Hello,

I am sending you the draft PI round 2. Please go through the label accept the changes you have no further comment on. The FDA comments bubble please respond to them in the bubble whether you agree or disagree. Do not submit anything to the NDA until we have finalized the labeling.

Please respond to us by **December 8, 2017**.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
12/06/2017

## Jairath, Meghna

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**From:** Jairath, Meghna  
**Sent:** Thursday, November 30, 2017 4:29 PM  
**To:** Mueller, Gilbert  
**Subject:** IR Carton and Container NDA-205598

**Importance:** High

### IR NDA 205598 Carton and Container

Hello,  
Please see our comments below and respond by 12/4/17.

1. Container Label and Carton Labeling – In accordance with 21 CFR 201.51, add a net quantity statement, such as “One Pouch” to the principal display panel. In addition, ensure the net quantity statement is not in close proximity to the strength statement to prevent the risk of numerical confusion.
2. Demonstration Kit – The revised container label and carton labeling still lacks sufficient differentiation when compared to the proposed labeling of the product intended for distribution and administration. We recommend the revisions below to improve differentiation, add clarity, and mitigate any confusion.
  - a. Container Label
    - i. Consider changing the font or background color to red for the statements, “DEMONSTRATION POUCH” and “CONTAINS NO MEDICINE.”
    - ii. Decrease the prominence of the proprietary name, Macrilen.
    - iii. Remove (b) (4) the contents do not contain macimorelin and is not intended for oral consumption.
    - iv. Add the important warning statement, “Not for human use” to the principal display panel and back panel of the pouch.
  - b. Carton Labeling
    - i. See 1.a.
    - ii. Remove the statements, “ (b) (4) .” and “ (b) (4) .”

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
12/01/2017

## Jairath, Meghna

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**From:** Jairath, Meghna  
**Sent:** Wednesday, November 22, 2017 7:55 PM  
**To:** Mueller, Gilbert  
**Subject:** NDA 205598 Round 1 Package Insert  
**Attachments:** FDA Round1 NDA 205598 PI.doc

**Importance:** High

Hello,

I am sending you the draft PI. Please go through the label accept the changes you have no further comment on. The FDA comments bubble please respond to them in the bubble whether you agree or disagree. Do not submit anything to the NDA until we have finalized the labeling.

Please respond to us by November 29, 2017.

Thanks,  
Meghna

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

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/s/  
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MEGHNA M JAIRATH  
11/27/2017

## Jairath, Meghna

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**From:** Jairath, Meghna  
**Sent:** Tuesday, November 21, 2017 9:55 AM  
**To:** Mueller, Gilbert  
**Subject:** IR Carton and Container NDA-205598

Information Request  
NDA 205598

Hello,  
Please review our comment below and respond to us by November 28, 2017.

1. Container Label – For added clarity and to mitigate any confusion, and to align labeling with similar currently approved products, revise the following:
  - a. On the principal display panel of the pouch (front),
    - i. change (b) (4) to “for oral solution”
    - ii. change “(b) (4)” to “60 mg”
    - iii. remove “(b) (4)”
    - iv. change “(b) (4)” to “Must administer dose within 30 minutes after reconstitution. Discard unused portion.”
  - b. On the back panel of the pouch,
    - i. Remove (b) (4)
    - ii. add “Each pouch contains: 60 mg macimorelin (equivalent to 68 mg macimorelin acetate), which corresponds to 60 mg/120 mL (0.5 mg/mL), when reconstituted”
2. Carton Labeling
  - a. See. 1.a. and 1.b.
  - b. On the back panel of the carton, change “granules for oral solution” to “for oral solution”
3. Demonstration Kit – The container label and carton labeling lacks sufficient differentiation when compared to the proposed labeling of the product intended for distribution and administration. To help mitigate any confusion and prevent potential medication errors (i.e., inadvertent administration of an unintended substance), revise the font type, size, or color of the labeling to further differentiate the demonstration kit from the product intended for distribution and administration. In addition, add the following important statement to the back panel of the pouch (container label) in bold font: **“Demonstration Pouch. CONTAINS NO MEDICINE.”**

1. Thanks,
2. Meghna

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/s/  
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MEGHNA M JAIRATH  
11/21/2017

## Jairath, Meghna

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**From:** Jairath, Meghna  
**Sent:** Monday, November 20, 2017 2:05 PM  
**To:** Mueller, Gilbert  
**Subject:** Macrilen (macimorelin acetate) NDA 205598 RCM 2017-1345: Information Request

**Follow Up Flag:** Follow up  
**Flag Status:** Flagged

Information Request  
NDA 205598

We refer to your 505(b)(1) NDA class 2 resubmission for Macrilen granules for oral solution, under NDA 205598, submitted on June 30, 2017. We note container and carton labeling for a proposed Demonstration Kit. Please respond to the following information requests:

### Demonstration Kit

1. The principal display panel on both container and carton labeling states, “**CONTAINS NO MEDICINE.**” However, it is unclear if the demonstration pouch (container label) will contain any substance. Please clarify if you intend for the demonstration pouch to be empty, or if it will contain a substance of some kind and specify the intended contents.
2. It is unclear from your submission who will have access to the Demonstration Kit and who will perform the demonstration. To better inform our review, please clarify who you intend will perform the demonstration (outlining in detail the specific steps of the demonstration), who will have access to the Demonstration Kit, and if the Demonstration Kit will be readily available to healthcare professionals in their daily practice.

Please respond to this information request and return comments as soon as possible, but no later than close of business **Tuesday, November 21, 2017.**

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
11/20/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 205598

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Aeterna Zentaris GmbH  
c/o Aeterna Zentaris Inc.  
315 Sigma Drive, Suite 302D  
Summerville, SC 29486

ATTENTION: Michael Ward  
President and CEO

Dear Mr. Ward:

Please refer to your resubmission to New Drug Application (NDA) dated and received June 30, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Macimorelin Acetate Granules for Oral Solution, 60 mg.

We also refer to your correspondence, dated and received October 11, 2017, requesting a reconsideration of your proposed proprietary name, Macrilen.

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

If any of the proposed product characteristics as stated in your above 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/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Deveonne Hamilton-Stokes, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2253. For any other information regarding this application, contact Abolade Adeolu, Regulatory Project Manager, in the Office of New Drugs at (301) 796-4264.

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

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/s/  
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DANIELLE M HARRIS on behalf of TODD D BRIDGES  
11/15/2017



NDA 205598

**PROPRIETARY NAME  
ACKNOWLEDGEMENT**

Aeterna Zentaris GmbH  
c/o Aeterna Zentaris Inc.  
315 Sigma Drive, Suite 302D  
Summerville, SC 29486

ATTENTION: Michael Ward  
President and CEO

Dear Mr. Ward:

Please refer to your resubmission to New Drug Application (NDA) dated and received June 30, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Macimorelin Acetate Granules for Oral Solution, 0.5 mg/mL.

We acknowledge receipt of your correspondence, dated and received October 11, 2017, requesting a reconsideration of your proposed proprietary name, Macrilen.

The user fee goal date is January 9, 2018.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Deveonne Hamilton-Stokes, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2253. For any other information regarding this application, contact Abolade Adeolu, Regulatory Project Manager, in the Office of New Drugs at (301) 796-4264.

Sincerely,

*{See appended electronic signature page}*

Deveonne Hamilton-Stokes, RN, BSN, MA  
Safety Regulatory Project Manager  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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DEVEONNE G HAMILTON-STOKES  
10/26/2017

**From:** Jairath, Meghna  
**To:** [Grandpierre-Verhees, Cordula](#)  
**Subject:** IR NDA 205598  
**Date:** Friday, October 13, 2017 8:43:52 AM  
**Attachments:** [InfoRequestGrowthHormoneMeasure.doc](#)

---

Hello,

Please view the attachment for our IR.  
Please send us a response by October 20, 2017.

Thanks,  
Meghna

In the End of Review meeting for NDA 205598 on March 6, 2015, you accepted our recommendation to develop and validate the assay to measure serum growth hormone concentrations according to the draft bioanalytical guidance (<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf>). See meeting minutes dated April 1, 2015, Pages 6 and 7 of 28. However, the validation report (08-aezs-130-ids-isys-hgh-with-amend-1-7.pdf) for Study AEZS-130-052 to measure serum growth hormone concentration is not consistent with the recommendations of the draft bioanalytical guidance. Provide clarifications for the following issues:

| <b>Study AEZS-130-052 did</b>                                                                                                                                   | <b>2013 FDA Draft Bioanalytical Guidance Recommends</b>                                                                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sparse calibrators of 2 concentrations (0.185 and 19.662 ng/mL)                                                                                                 | 6 non-zero calibrators                                                                                                                                         |
| No duplicate calibrators                                                                                                                                        | Duplicate calibrators                                                                                                                                          |
| Standard curve not include LLOQ (< 0.05 ng/mL) and the measured serum growth hormone concentration up to 60 ng/mL                                               | Standard curve includes the LLOQ covering the entire measured concentration range                                                                              |
| Calibrators in horse serum; absence of justification for the use of horse serum for biological matrix                                                           | Calibrators in human serum to match sample matrix                                                                                                              |
| Absence of information on calibrators show no measurable endogenous human growth hormone                                                                        | The biological matrix of calibrators shows no measurable endogenous human growth hormone.                                                                      |
| Absence of information on the analyte-free biological matrix should have no matrix effect or interference when compared to the biological matrix of calibrators | The analyte-free biological matrix should have no matrix effect or interference when compared to the biological matrix of calibrators.                         |
| QC samples, at 2.59, 6.74, and 12.4 ng/mL, do not cover the entire concentration range observed in the study.                                                   | QC at low, mid, and high concentrations: low QC should be within 3 times the LLOQ, midrange QC, and QC at high end of the expected study sample concentrations |

Did all of the following facilities use the validated bioanalytical assay (08-aezs-130-ids-isis-hgh-with-amend-1-7.pdf) and procedures to measure the serum growth hormone concentrations for samples from Study AEZS-130-052?

-  (b) (4)
- 
- 

Additional Question:

For Study AEZS-130-054 report Page 47 of 68, Figure 2, what are the reasons for the exposure of growth hormone resulting from administration of 2 mg/kg macimorelin is lower than the exposure of growth hormone resulting from either administration of 0.5 mg/kg macimorelin or 1 mg/kg macimorelin?

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/s/  
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MEGHNA M JAIRATH  
10/16/2017

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Thursday, September 28, 2017 3:20 PM  
**To:** GMueller@aezsinc.com  
**Cc:** Jairath, Meghna; Adeolu, Abolade  
**Subject:** NDA 205598

Gilbert-

The submission did not include subgroup analyses by country/geographic region that are required as part of an NDA. Also, we were not able to locate a variable that identifies subjects' country/geographic location in the submitted datasets. Please provide the subgroup analysis results, data on geographic location, and supporting analysis programs by October 12, 2017.

Thanks,

Bola Adeolu, R.Ph., MS, MBA  
Senior Regulatory Project Manager,  
FDA/CDER/OND  
Division of Metabolism and Endocrinology Products  
White Oak, Bldg 22, Rm 3121  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/  
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ABOLADE ADEOLU  
09/28/2017



NDA 205598

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

Aeterna Zentaris GmbH  
c/o Aeterna Zentaris Inc.  
315 Sigma Drive, Suite 302D  
Summerville, SC 29486

ATTENTION: Michael Ward  
Chief Executive Officer

Dear Mr. Ward:

Please refer to your New Drug Application (NDA) dated and received June 30, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Macimorelin Acetate Granules for Oral Solution, 0.5 mg/mL (b) (4).

We also refer to your correspondence, dated and received June 30, 2017, requesting review of your proposed proprietary name, Macrilen.

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

The proposed proprietary name, Macrilen, may be confused with Marcillin (ampicillin), due to orthographic similarities and overlapping product characteristics.

Orthographically, this name pair is similar in length (8 letters vs. 9 letters) when scripted. The prefixes of this name pair begin with the same letter strings (“Ma”), the infixes contain the same letters (“crl” vs. “rcil”), and the suffixes of this name pair, “len” vs. “lin,” look similar when scripted. We note that Marcillin has an additional upstroke letter “l,” which is not present in Macrilen. However, given the orthographic similarity of the names, this difference may not be sufficient to mitigate the risk of confusion.

The similarity of this name pair is further supported by FDA’s Phonetic and Orthographic Computer Analysis (POCA)<sup>1</sup> search results, which calculates a combined orthographic and phonetic score of 78% for this name pair (orthographic only score of 82%). This further suggests that the names Macrilen and Marcillin have high similarity and pose a risk for confusion.

In addition to orthographic similarities between this name pair, the products share overlapping

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<sup>1</sup> POCA search conducted on August 23, 2017. POCA tool updated to incorporate a revised orthographic algorithm.

product characteristics, which increase the potential for wrong drug errors. Specifically, both products have a single route of administration (*oral*) and share a similar dosage form that must be reconstituted prior to administration (*granules for oral solution* vs. *powder for oral suspension*). The dose for Macrilen is 0.5 mg/kg, whereas the dose for Marcillin depends on the indication (250 mg, 500 mg, 3.5 g, 50 mg/kg, or 100 mg/kg). We note that there is the potential for a 100-fold numerical similarity in dose (0.5 mg/kg vs. 50 mg/kg/day).

We acknowledge that Macrilen and Marcillin have different strengths (0.5 mg/mL vs. 500 mg and 250 mg/5 mL) and dosing frequency (*one-time dose for diagnostic purposes* vs. *one to four times daily, depending on the indication and renal impairment*). However, our postmarketing experiences with other products suggest that name confusion can occur between similarly named products with differing strengths and frequency. For example, name confusion occurred between Prenexa and Ranexa despite differences in strength (Prenexa is a multi-ingredient product and typically written without the strength vs. Ranexa is available as 500 mg and 1,000 mg) and dosing frequency (Prenexa is dosed once daily and Ranexa is dosed twice daily).<sup>2</sup>

We acknowledge that Marcillin is a discontinued product. However, Marcillin is still identified in the commonly searched drug database Redbook and generic equivalents remain available in the marketplace. FDA is aware that prescribers may still use discontinued proprietary names to order generic equivalents in clinical practice for years after the brand name product is discontinued.<sup>3</sup> Hence, if a prescription for Macrilen is interpreted as Marcillin, the prescription can still be filled with a generically equivalent ampicillin product.

Therefore, based on orthographic similarity and overlapping product characteristics, we conclude there is a risk for name confusion between Macrilen and Marcillin.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

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

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

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<sup>2</sup> Institute for Safe Medication Practices. Safety briefs: Ranexa and Prenexa too similar. ISMP Med Saf Alert Community/Ambulatory Care. 2012; 11(3): 1-4.

<sup>3</sup> Tu, CM, Taylor, K, and Chai, G. Use of Proprietary Names by Prescribers for Discontinued Brand Drug Products With Existing Generic Equivalents. Drug Information Journal, published online August 21, 2012, available at <http://dij.sagepub.com/content/early/2012/08/21/0092861512456282.full.pdf+html>

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Deveonne Hamilton-Stokes, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2253. For any other information regarding this application, contact Abolade Adeolu, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4264.

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

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/s/  
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DANIELLE M HARRIS on behalf of TODD D BRIDGES  
09/25/2017



NDA 205598

**PROPRIETARY NAME  
ACKNOWLEDGEMENT**

Aeterna Zentaris GmbH  
c/o Aeterna Zentaris, Inc.  
315 Sigma Drive, Suite 302D  
Summerville, SC 29486

ATTENTION: Philip A. Theodore  
Senior Vice President, Chief Administrative Officer and General Counsel

Dear Mr. Theodore:

Please refer to your New Drug Application (NDA) dated November 4, 2013 and received November 5, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Macimorelin Acetate Solution, 0.5 mg/mL.

We acknowledge receipt of your correspondence, dated and received June 30, 2017, requesting a review of your proposed proprietary name, Macrilen.

The user fee goal date for your proposed proprietary name is September 28, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Deveonne Hamilton-Stokes, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2253. For any other information regarding this application, contact Abolade Adeolu, Regulatory Project Manager, in the Office of New Drugs at (301) 796-4264.

Sincerely,

*{See appended electronic signature page}*

Deveonne Hamilton-Stokes, RN, BSN, MA  
Safety Regulatory Project Manager  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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DEVEONNE G HAMILTON-STOKES  
07/31/2017



NDA 205598

**ACKNOWLEDGE –  
CLASS 2 RESUBMISSION**

Aeterna Zentaris, Inc.  
Attention: Philip A. Theodore  
Senior VP, Chief Administrative Officer & General Counsel  
315 Sigma Drive, Suite 302D  
Summerville, SC 29486

Dear Mr. Theodore:

We acknowledge receipt on June 30, 2017, of your June 30, 2017, resubmission to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for macimorelin acetate granules for oral solution. (We note that the cover letter for this submission is dated June 23, 2017.)

We consider this a complete, class 2 response to our November 5, 2014, action letter. Therefore, the user fee goal date is December 30, 2017.

If you have any questions, call me at (301) 796-4264.

Sincerely,

*{See appended electronic signature page}*

Abolade (Bola) Adeolu, RPh, MS, MBA  
Regulatory Project Manager  
Division of Metabolism & Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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ABOLADE ADEOLU  
07/10/2017

# ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION <sup>1</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NDA # 205598                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | NDA Supplement #<br>BLA Supplement # | If NDA, Efficacy Supplement Type:<br><i>(an action package is not required for SE8 or SE9 supplements)</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Proprietary Name: Macrilen<br>Established/Proper Name: macimorelin acetate<br>Dosage Form: granules (b) (4)                                                                                                                                                                                                                                                                                                                                                                                    |                                      | Applicant: Aeterna Zentaris GmbH<br>Agent for Applicant (if applicable): Kerin Ablashi at Biologics Consulting Group, Inc                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| RPM: Abolade (Bola) Adeolu                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                      | Division: Metabolism & Endocrinology Products                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)<br>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)<br><br>BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)<br>Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)                                                                                                      |                                      | <b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <div style="margin-left: 20px;"> <input type="checkbox"/> No changes<br/> <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)<br/>           Date of check:         </div> <p style="margin-left: 20px;"><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p> |
| ❖ Actions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>November 5, 2014</u></li> </ul>                                                                                                                                                                                                                                                                                                                                                                       |                                      | <input type="checkbox"/> AP <input type="checkbox"/> TA <input checked="" type="checkbox"/> CR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                        |                                      | <input checked="" type="checkbox"/> None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?<br>Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____ |                                      | <input type="checkbox"/> Received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| ❖ Application Characteristics <sup>3</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

<sup>1</sup> 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.

<sup>2</sup> 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).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority  
Chemical classification (new NDAs only): Type 1 - NME  
(confirm chemical classification at time of approval)

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

NDAs: Subpart H

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

Subpart I

- ☐ Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- ☐ Approval based on animal studies

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

Comments:

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

| Action Letters                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ❖ Copies of all action letters (including approval letter with final labeling)                                                                                                                                                                           | Action(s) and date(s)                                                                                                                                                                                                                                                                                             |
| Labeling                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                   |
| ❖ Package Insert (write submission/communication date at upper right of first page of PI)                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                   |
| <ul style="list-style-type: none"> <li>Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)</li> </ul>                                                                                                 | <input type="checkbox"/> Included                                                                                                                                                                                                                                                                                 |
| <ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>                                                                                                                                                                   | <input checked="" type="checkbox"/> Included                                                                                                                                                                                                                                                                      |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)                                                                                          | <input type="checkbox"/> Medication Guide<br><input type="checkbox"/> Patient Package Insert<br><input type="checkbox"/> Instructions for Use<br><input type="checkbox"/> Device Labeling<br><input checked="" type="checkbox"/> None                                                                             |
| <ul style="list-style-type: none"> <li>Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)</li> </ul>                                                                                                 | <input type="checkbox"/> Included                                                                                                                                                                                                                                                                                 |
| <ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>                                                                                                                                                                   | <input type="checkbox"/> Included                                                                                                                                                                                                                                                                                 |
| ❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)                                                                                                        |                                                                                                                                                                                                                                                                                                                   |
| <ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>                                                                                                                                                                             | <input checked="" type="checkbox"/> Included                                                                                                                                                                                                                                                                      |
| ❖ Proprietary Name                                                                                                                                                                                                                                       | Acceptable: Letter: 1/27/2014<br>Review: 1/16/2014                                                                                                                                                                                                                                                                |
| <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (indicate date(s))</li> <li>Review(s) (indicate date(s))</li> </ul>                                                                                                     |                                                                                                                                                                                                                                                                                                                   |
| ❖ Labeling reviews (indicate dates of reviews)                                                                                                                                                                                                           | RPM: 1/15/2014<br>DMEPA: 8/11/2014;<br>8/5/2014; 5/16/2014; 2/26/2014<br>DMPP/PLT (DRISK):<br><input checked="" type="checkbox"/> None<br>OPDP: 10/24/2014<br>SEALD: <input checked="" type="checkbox"/> None<br>CSS: <input checked="" type="checkbox"/> None<br>Other: <input checked="" type="checkbox"/> None |
| Administrative / Regulatory Documents                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                   |
| ❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting (indicate date of each review) All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee                                                                             | 1/15/2014<br><br>Not a (b)(2)                                                                                                                                                                                                                                                                                     |
| ❖ NDAs only: Exclusivity Summary (signed by Division Director)                                                                                                                                                                                           | <input type="checkbox"/> Included                                                                                                                                                                                                                                                                                 |
| ❖ Application Integrity Policy (AIP) Status and Related Documents<br><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> |                                                                                                                                                                                                                                                                                                                   |
| <ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>                                                                                                                                                                                | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No                                                                                                                                                                                                                                               |

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

|                                                                                                                                                                                                                                                                                                                       |                                                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>This application is on the AIP           <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo <i>(indicate date)</i></li> <li>If yes, OC clearance for approval <i>(indicate date of clearance communication)</i></li> </ul> </li> </ul> | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No<br><br><input type="checkbox"/> Not an AP action |
| ❖ Pediatrics <i>(approvals only)</i> <ul style="list-style-type: none"> <li>Date reviewed by PeRC _____<br/>If PeRC review not necessary, explain: _____</li> </ul>                                                                                                                                                   | Did not go to PeRC because of orphan designation                                                                     |
| ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) <i>(do not include previous action letters, as these are located elsewhere in package)</i>                                | Included                                                                                                             |
| ❖ 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)                                                                             |                                                                                                                      |
| ❖ Minutes of Meetings                                                                                                                                                                                                                                                                                                 |                                                                                                                      |
| <ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i></li> </ul>                                                                                                                                                                              | <input checked="" type="checkbox"/> N/A or no mtg                                                                    |
| <ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting <i>(indicate date of mtg)</i></li> </ul>                                                                                                                                                                                                                   | <input checked="" type="checkbox"/> No mtg                                                                           |
| <ul style="list-style-type: none"> <li>EOP2 meeting <i>(indicate date of mtg)</i></li> </ul>                                                                                                                                                                                                                          | <input checked="" type="checkbox"/> No mtg                                                                           |
| <ul style="list-style-type: none"> <li>Mid-cycle Communication <i>(indicate date of mtg)</i></li> </ul>                                                                                                                                                                                                               | 4/16/2014                                                                                                            |
| <ul style="list-style-type: none"> <li>Late-cycle Meeting <i>(indicate date of mtg)</i></li> </ul>                                                                                                                                                                                                                    | 7/23/2014                                                                                                            |
| <ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i></li> </ul>                                                                                                                                                                                  |                                                                                                                      |
| ❖ Advisory Committee Meeting(s)                                                                                                                                                                                                                                                                                       | No AC meeting                                                                                                        |
| <ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>                                                                                                                                                                                                                                               |                                                                                                                      |
| <b>Decisional and Summary Memos</b>                                                                                                                                                                                                                                                                                   |                                                                                                                      |
| ❖ Office Director Decisional Memo <i>(indicate date for each review)</i>                                                                                                                                                                                                                                              | 11/5/2014                                                                                                            |
| Division Director Summary Review <i>(indicate date for each review)</i>                                                                                                                                                                                                                                               | 11/5/2014                                                                                                            |
| Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>                                                                                                                                                                                                                                            | 10/31/2014                                                                                                           |
| PMR/PMC Development Templates <i>(indicate total number)</i>                                                                                                                                                                                                                                                          | <input checked="" type="checkbox"/> None                                                                             |
| <b>Clinical</b>                                                                                                                                                                                                                                                                                                       |                                                                                                                      |
| ❖ Clinical Reviews                                                                                                                                                                                                                                                                                                    |                                                                                                                      |
| <ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) <i>(indicate date for each review)</i></li> </ul>                                                                                                                                                                                               | <input checked="" type="checkbox"/> No separate review                                                               |
| <ul style="list-style-type: none"> <li>Clinical review(s) <i>(indicate date for each review)</i></li> </ul>                                                                                                                                                                                                           | 9/9/2014; 12/20/2013                                                                                                 |
| <ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i></li> </ul>                                                                                                                                                                                     | <input checked="" type="checkbox"/> None                                                                             |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>                                                | Page 15 of 9/9/2014 clinical review                                                                                  |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>                                                                                                                                                                                                   | <input checked="" type="checkbox"/> None                                                                             |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>                                                                                                                                                                                                            | <input checked="" type="checkbox"/> N/A                                                                              |

|                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                          |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| ❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul> | 7/3/2014                                                                 |
| ❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )                                                                                                                                                                                                                                                                                                               | 9/9/2014                                                                 |
| <b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None                                                                                                                                                                                                                                                                                                                                                 |                                                                          |
| ❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                | <input type="checkbox"/> No separate review                              |
| Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                              |                                                                          |
| <b>Biostatistics</b> <input type="checkbox"/> None                                                                                                                                                                                                                                                                                                                                                                    |                                                                          |
| ❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                    | <input checked="" type="checkbox"/> No separate review                   |
| Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                            | <input checked="" type="checkbox"/> No separate review                   |
| Statistical Review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                                        | 7/9/2014; 12/31/2013                                                     |
| <b>Clinical Pharmacology</b> <input type="checkbox"/> None                                                                                                                                                                                                                                                                                                                                                            |                                                                          |
| ❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                          | <input checked="" type="checkbox"/> No separate review                   |
| Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                  | <input checked="" type="checkbox"/> No separate review                   |
| Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                              | 8/7/2014; 7/16/2014; 12/9/2013                                           |
| ❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )                                                                                                                                                                                                                                                                                                                        | <input checked="" type="checkbox"/> None requested                       |
| <b>Nonclinical</b> <input type="checkbox"/> None                                                                                                                                                                                                                                                                                                                                                                      |                                                                          |
| ❖ Pharmacology/Toxicology Discipline Reviews                                                                                                                                                                                                                                                                                                                                                                          |                                                                          |
| • ADP/T Review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                                            | 10/31/2014 (2)                                                           |
| • Supervisory Review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                                                      | <input checked="" type="checkbox"/> No separate review                   |
| • Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                      | 6/5/2014; 12/6/2013                                                      |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                 | <input checked="" type="checkbox"/> None                                 |
| ❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                                                                                                           | <input checked="" type="checkbox"/> No carc                              |
| ❖ ECAC/CAC report/memo of meeting                                                                                                                                                                                                                                                                                                                                                                                     | <input checked="" type="checkbox"/> None<br>Included in P/T review, page |
| ❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )                                                                                                                                                                                                                                                                                                                                  | <input checked="" type="checkbox"/> None requested                       |

| Product Quality <input type="checkbox"/> None                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ❖ Product Quality Discipline Reviews                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                       |
| • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                       | <input checked="" type="checkbox"/> No separate review                                                                                                                                |
| • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                          | <input checked="" type="checkbox"/> No separate review                                                                                                                                |
| • Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>                                                                                                                                                                                                                                          | 9/15/2014; 7/3/2014; 12/19/2013<br>Biopharm: 6/17/2014                                                                                                                                |
| ❖ Microbiology Reviews<br><input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i><br><input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>                                             | 11/6/2013                                                                                                                                                                             |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>                                                                                                                                                                                                                             | <input checked="" type="checkbox"/> None                                                                                                                                              |
| ❖ Environmental Assessment (check one) (original and supplemental applications)                                                                                                                                                                                                                                                                      |                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>                                                                                                                                                           | See review dated 7/3/2014, page 80                                                                                                                                                    |
| <input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>                                                                                                                                                                                                                                                                             |                                                                                                                                                                                       |
| <input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>                                                                                                                                                                                                                                               |                                                                                                                                                                                       |
| ❖ Facilities Review/Inspection                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                       |
| <input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i> | 11/4/2014<br><input checked="" type="checkbox"/> Acceptable<br><input type="checkbox"/> Withhold recommendation<br><input type="checkbox"/> Not applicable                            |
| <input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>                                                                                                                                                                                              | Date completed:<br><input type="checkbox"/> Acceptable<br><input type="checkbox"/> Withhold recommendation                                                                            |
| ❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>                                                                                                                                                                                                                                                                         | <input type="checkbox"/> Completed<br><input type="checkbox"/> Requested<br><input type="checkbox"/> Not yet requested<br><input checked="" type="checkbox"/> Not needed (per review) |

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

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

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/s/  
-----

ABOLADE ADEOLU  
11/05/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Thursday, September 04, 2014 4:22 PM  
**To:** Kerin Ablashi (kablashi@bcg-usa.com)  
**Cc:** Adeolu, Abolade  
**Subject:** macimorelin

Dear Kerin,

Please confirm or correct the following conclusions from your latest submission.

The GH test for subject 609 performed from Visit 2 when they received macimorelin was performed using a serum sample.

The GH tests for subjects 603 (visit 2), 604 (visit 3), 801 (visit 3) and 802 (visit 2) when they received macimorelin were performed on plasma samples. No serum samples were available for these subjects.

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, Bldg 22, Rm 3121  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/  
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ABOLADE ADEOLU  
09/05/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Tuesday, August 19, 2014 8:55 AM  
**To:** Kerin Ablashi (kablashi@bcg-usa.com)  
**Cc:** Adeolu, Abolade  
**Subject:** NDA 205598

Dear Kerin,

The following items refer to your response 0019 (20) dated 08/12/2014.

Confirm that at the time subjects 0307 (page 4) and 0629 (page 9) were enrolled in the study L-Arg was not an approved diagnostic inclusion criteria listed in the study protocol and it was only included under Amendment 5 dated 13-Jan-2011 well after the patients had already completed their role in the study.

Explain how subject 0701 (page 15) who had two pituitary hormone deficiencies and was receiving two hormone replacement therapies without a pretest GHST was not picked up as a violation of the eligibility criteria during the monitoring of the raw data by <sup>(b) (4)</sup> or AEZS?

Thanks,  
Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, Bldg 22, Rm 3121  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

Tel: 301 796-4264

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ABOLADE ADEOLU  
08/19/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Thursday, July 17, 2014 3:07 PM  
**To:** Kerin Ablashi (kablashi@bcg-usa.com)  
**Cc:** Adeolu, Abolade  
**Subject:** NDA 205598: labeling

Dear Kerin,

Please find attached our initial comments/edits on labeling for the macimorelin application.

Kindly acknowledge email and let me know when to expect your response.



Initial Comments

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, Bldg 22, Rm 3121  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

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ABOLADE ADEOLU  
07/17/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Wednesday, June 25, 2014 1:19 PM  
**To:** Kerin Ablashi (kablashi@bcg-usa.com)  
**Cc:** Adeolu, Abolade; Chen, Elizabeth  
**Subject:** NDA 205598

**Importance:** High

Dear Kerin,

Please respond to the following by June 30, 2014

Bioanalytical Report AEZS-130/110002181 for Study AEZS 130-047's Tab 5 (Page 15 of 24) shows that the -0.25 and 0 hours plasma samples have quantifiable macimorelin concentrations for the following patients:

- Patient 1029 at -0.25 hour
- Patients 1032, 1142, 1702, 1703, 1704, 1705, 1706, 1714, and 1715 at 0 hour
- 

These predose plasma macimorelin concentrations are > than 5 percent of the macimorelin  $C_{\max}$  value in the corresponding patient's data except Patient 1032. Explain these predose plasma macimorelin concentrations. Bioanalytical Report EP01572/070016034 for Study ARD-0705-003's Tab III.9 (with meal; Page 24) shows that Participant 3 has quantifiable plasma macimorelin concentration at 0 hour and Participant 4 has quantifiable plasma macimorelin concentration at -0.25 hour. These predose plasma macimorelin concentrations are > than 5 percent of the macimorelin  $C_{\max}$  value for Participants 3 and 4. Explain these predose plasma macimorelin concentrations.

Bioanalytical Report EP01572/070016034 for Study ARD-0705-003's Tab III.10 (without meal; Page 25) shows that Participants 8 and 12 have quantifiable plasma macimorelin concentration at -0.25 hour. Also, Participants 3, 6, and 8 have quantifiable plasma macimorelin concentration at 0 hour. Explain that the predose plasma macimorelin concentration at 0 hour is > than 5 percent of the macimorelin  $C_{\max}$  value for Participant 6.

Please submit to us the bioanalytical report for the determination of serum growth hormone concentration for Study AEZS-130-047 that we requested on June 20, 2014.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, Bldg 22, Rm 3121  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

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ABOLADE ADEOLU  
06/25/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Friday, June 20, 2014 7:03 AM  
**To:** Kerin Ablashi (kablashi@bcg-usa.com)  
**Cc:** Adeolu, Abolade; Chen, Elizabeth  
**Subject:** NDA 205598

**Importance:** High

Dear Kerin,

Please respond to the following requests by June 30, 2014:

- Inform the location of the bioanalytical report for the determination of serum growth hormone concentration for Study AEZS-130-047 or submit the bioanalytical report.
- Study ARD-0705-003's bioanalytical report's (EP10572/070016034) Pages 2 and 3 show the following inconsistencies in comparison with Tab III.9 and Tab III.10 (Pages 24 and 25):
  - 476 plasma samples vs. 960 plasma samples
  - 12 subjects vs. 16 subjects
  - peak plasma macimorelin concentrations range of 2.9 – 21.9 ng/mL vs. 2.18 – 9.66 ng/mL when administered with food
  - peak plasma macimorelin concentrations range of 2.2 – 20.1 ng/mL vs. 3.32 – 21.9 ng/mL when administered without food
  - The concentration vs. time plots of Pages 2 and 33 for Day 1 (with food) are inconsistent with Tab III.9 since the Day 1 plot shows plasma macimorelin concentrations above 10 ng/mL, whereas the highest is 9.66 ng/mL.
  - The concentration vs. time plots of Pages 3 and 33 for Day 4 (without food) are inconsistent with Tab III.10 since the Day 4 plot shows peak plasma macimorelin concentrations below 20 ng/mL, whereas the highest is 21.9 ng/mL.
  - Summary of Biopharmaceutic Studies, Module 2.7.1 page 6 states: "A single urine sample approximately 4 hours post-dosing was collected. Macimorelin urine concentration (mean  $\pm$  SD) was  $182 \pm 132$  ng/mL (median = 154 ng/mL, range = 11 to 517 ng/mL) when administered without food and  $82 \pm 41$  ng/mL (median = 77 ng/mL, range = 16 to 180 ng/mL) when administered with food." Also Study ARD-0705-003's bioanalytical report's (EP10572/070016034) Pages 26 Tab III.11 shows the postdose urine macimorelin concentrations. However, Study ARD-0705-003's report Page 42 (82) states "A single urine sample approx. 4 hours post-dosing was collected and ARD-07 was measured in it. Measurable amounts were detected in urine but could not be quantified in this study."

Kindly acknowledge receipt of this email. Also, I will be out of the office when you respond, so I have copied my colleague who will be covering me for emergencies.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, Bldg 22, Rm 3121  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

Tel: 301 796-4264

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ABOLADE ADEOLU  
06/20/2014

## Adeolu, Abolade

---

**From:** Adeolu, Abolade  
**Sent:** Monday, June 16, 2014 1:52 PM  
**To:** Kerin Ablashi (kablashi@bcg-usa.com)  
**Subject:** NDA 205598

Dear Kerin,

Please provide a sample of the product container/closure system, the 50 x 72 mm (b) (4) made of (b) (4) aluminum foil. Kindly send us some (5-10 samples). They can be filled or unfilled. We would like to check the quality.

Kindly acknowledge receipt of this email, and let me know when to expect the package

Thanks,  
Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, Bldg 22, Rm 3121  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

Tel: 301 796-4264

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ABOLADE ADEOLU  
06/16/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Thursday, June 05, 2014 12:48 PM  
**To:** Kerin Ablashi (kablashi@bcg-usa.com)  
**Cc:** Adeolu, Abolade  
**Subject:** Macrilen

Dear Kerin,

We recommend that the following be implemented :

- A. Container label
  - a. To mitigate any confusion and minimize the risk of dosing errors, please revise the statement, (b) (4) to the following:  
*"(corresponding to 60 mg per 120 mL, when reconstituted)"*
- B. Carton labeling
  - a. To mitigate any confusion and minimize the risk of dosing errors, please revise the statement, (b) (4) to the following:  
*"(corresponding to 60 mg per 120 mL, when reconstituted)"*

Kindly acknowledge receipt of this email.

Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, Bldg 22, Rm 3121  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

Tel: 301 796-4264

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ABOLADE ADEOLU  
06/05/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Friday, May 16, 2014 2:18 PM  
**To:** Kerin Ablashi (kablashi@bcg-usa.com)  
**Cc:** Adeolu, Abolade  
**Subject:** NDA 205598

Dear Kerin,

We recommend the following be implemented:

### A. Container Label

a. The established name for drug products should include the complete finished dosage form per Guidance: Container Labels and Carton Labeling, April 2013.

Include the finished dosage form (e.g., granules *for oral solution*) after the established name.

b. The established name is not ½ the size of the proprietary name and lacks prominence commensurate with the proprietary name. Increase the size and prominence of the established name (including the finished dosage form) taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

c. The concentration or product strength per milliliter (e.g., “0.5 mg per mL”) is located in the middle of the label, separated from the proprietary name and established name. Relocate the product strength so that it is listed below the proprietary name, established name, and finished dosage form. Additionally, increase the prominence of the strength to improve readability. Furthermore, revise the product strength as follows: “(b) (4)”.

The total drug content statement (e.g., “60 mg per 120 mL, when reconstituted”) may be listed after the strength per milliliter to minimize the risk of overdose when the entire pouch content is administered as a single dose.

d. Include the statement, “Product must be used within 30 minutes after preparation” on the container label as this is an important warning statement since a decrease in the active ingredient can be observed after 30 minutes of standing time at room temperature following reconstitution. If space permits, please include this statement on the principal display panel (PDP).

e. On the label, include the lot number in accordance with 21 CFR 201.10(i) and expiration date per Guidance: Container Labels and Carton Labeling, April 2013 as this is important information that may be overlooked by the user if the carton labeling is discarded. 1

### B. Carton labeling

a. See Section 4.2 A.a. through A.d and revise carton labeling accordingly.

b. The carton packaging is difficult to open and (b) (4). Please revise the packaging (b) (4) in order to make the process more user-friendly.

(b) (4)

Please acknowledge receipt of this email and let me know how soon to expect your response.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, Bldg 22, Rm 3121  
10903 New Hampshire Avenue,  
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ABOLADE ADEOLU  
05/16/2014

**Adeolu, Abolade**

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**From:** Adeolu, Abolade  
**Sent:** Thursday, May 08, 2014 12:05 PM  
**To:** Kerin Ablashi (kablashi@bcg-usa.com)  
**Cc:** Adeolu, Abolade  
**Subject:** NDA 205598

Kerin,

Clarify if there are any Drug Master Files for the container/closure system for your drug product. If so, provide a letter of authorization from the DMF holder to allow the Agency to review it.

Thanks,  
Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, Bldg 22, Rm 3121  
10903 New Hampshire Avenue,  
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ABOLADE ADEOLU  
05/09/2014



NDA 205598

**MID-CYCLE COMMUNICATION**

Biologics Consulting Group, Inc.  
Attention: Kerin Ablashi  
US Agent for Aeterna Zentaris GmbH  
400 N. Washington Street, Suite 100  
Alexandria, VA 22314

Dear Ms. Ablashi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Macrilen (macimorelin acetate granules) for oral solution.

We also refer to the teleconference between representatives of your firm and the FDA on April 16, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-4264.

Sincerely,

*{See appended electronic signature page}*

Abolade (Bola) Adeolu, RPh, MS, MBA  
Regulatory Project Manager  
Division of Metabolism & Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** April 16, 2014, from 9:00 to 10:00 AM

**Application Number:** NDA 205598  
**Product Name:** Macrilen (macimorelin acetate granules) for oral solution  
**Indication:** Diagnostic for adult growth hormone deficiency  
**Applicant Name:** Aeterna Zentaris GmbH

**Meeting Chair:** Jean-Marc Guettier, MD  
**Meeting Recorder:** Abolade (Bola) Adeolu

**FDA ATTENDEES**

Mary Parks, MD - Deputy Director, Office of Drug Evaluation II  
Jean-Marc Guettier, MD - Director (acting) Division of Metabolism & Endocrinology Products (DMEP)  
Dragos Roman, MD - Clinical Team Leader, DMEP  
Todd Bourcier, PhD - Nonclinical Supervisor, DMEP  
Jeffery Quinn, PhD - Nonclinical Reviewer, DMEP  
Immo Zadezensky, PhD - Clinical Pharmacology Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)  
Johnny Lau, PhD - Clinical Pharmacology Reviewer, DCPII, OCP  
Thomas Permutt, PhD - Director, Division of Biometrics II  
Mark Rothmann, PhD - Lead Mathematical Statistician, Division of Biometrics II  
Lan Huang, PhD - Statistical Reviewer, Division of Biometrics V  
Assadollah Noory, PhD - Biopharmaceutics Reviewer  
Naomi Redd, PharmD - Risk Management Analyst, Division of Risk Management  
Julie Van der Waag, MPH - Chief, Project Management Staff  
Abolade (Bola) Adeolu, RPh, MS, MBA - Regulatory Project Manager

**INDEPENDENT ASSESSOR**

So Hyun Kim, Eastern Research Group

**APPLICANT ATTENDEES**

Richard Sachse, Chief Scientific Officer / Chief Medical Officer  
Michael Teifel, Vice President Preclinical Development  
Rudi Martens, Vice President Pharmaceutical Operations  
Manfred Peukert, Vice President Medical Affairs  
Daniel Croteau, Director Medical Affairs  
Goswin Reuschenbach, Regulatory Consultant, Former local Head of Regulatory Affairs  
Kerin Ablashi, Consultant, Biologics Consulting Group (BCG)

## 1.0 INTRODUCTION

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

## 2.0 SIGNIFICANT ISSUES

### Statistics

1. Statistical significance was not achieved in the pre-planned primary analysis of the study. For the pre-planned primary analysis, the lower bound of the 99% confidence interval for the ROC AUC is  $<0.85$ , the pre-specified threshold.
2. There is a significant imbalance in race between the AGHD group and the matched control group. Two of 52 AGHD patients (4%) and 18 out of 48 matched controls (38%) are Black or African-American. Race may be a confounding factor for evaluating the diagnostic efficacy.
3. There is a significant imbalance in study site between the AGHD group and the matched control group. For example, no AGHD patients were enrolled from Sites 11 and 17, and most of the matched controls were enrolled from Sites 09, 10, 11 and 17. Site may be a confounding factor for evaluating the diagnostic efficacy.
4. The selected cutpoint was based on the same data that was used to determine its sensitivity and specificity. Therefore, the estimates of sensitivity and specificity may tend to overstate the truth. However, it is not clear if the sensitivity of 0.81 and specificity of 0.92 obtained in Study AEZS-130-047 can be reproduced in another study.

### Clinical Pharmacology

5. We are reviewing your submission dated April 11, 2014, with your response to our information request dated March 31, 2014.

### **3.0 INFORMATION REQUESTS**

Submit a multiple column table that describes vertically the individual baseline patient characteristics under the following column titles : subject's ID (column 1) , subject's age (column 2), IGF-1 values (list range if more than one value) (column 3), normal IGF-1 range for each patient (column 4), GH stimulation test results (columns 5-8) and presence or absence of other pituitary deficiencies (a column for each pituitary hormone: gonadotropins, TSH, ACTH, AVP and a description of the specific criteria used for diagnosis). The columns for GH stimulation tests (columns 5-8) should be: L-ARG + GHRH (<4.1 µg/L); ITT (<5.0 µg/L), glucagon (< 3.0 µg/L), and arginine (< 0.4 µg/L).

### **4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

At this time, there are no major safety concerns identified and there is currently no need for a REMS.

### **5.0 ADVISORY COMMITTEE MEETING**

None anticipated

### **6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES**

Discussion of labeling/PMR/PMC/REMS will be initiated July 18, 2014.

Late cycle meeting with Aeterna Zentaris GmbH is scheduled for July 23, 2014 from 9:00 to 10:00 AM.

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/s/  
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ABOLADE ADEOLU

04/24/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Wednesday, April 09, 2014 12:57 PM  
**To:** Pelliccione, Nick (NPelliccione@aezsinc.com)  
**Cc:** Adeolu, Abolade  
**Subject:** NDA 205598(macimorelin)

**Importance:** High

Dear Nick,

Please provide responses to the following CMC comments by April 22, 2014.

1. Provide certificates of analysis for starting materials and reagents, including all specifications and identification of suppliers.
2. Provide additional information on (b) (4) the drug substance observed in the NMR spectra. (b) (4)
3. Correct the peak assignments (b) (4) NMR spectra given in Section 3.1, as for example, regarding (b) (4). The NMR assignments also do not agree with those given under the release method for identity by NMR.
4. As communicated in the 74-day letter, identification of (b) (4) is required based on the proposed acceptance limits. Provide an update on your progress and an estimated time for completion of this task.
5. An impurity, designated as (b) (4), is identified in the MCase genotoxicity assessment report as containing a structural alert for mutagenicity. Where is the (b) (4) formed, either in the synthetic pathway or the drug product? What is the likelihood that this impurity is found in the drug substance or drug product? Indicate if it is detectable and determine the amount of this impurity in the drug substance and relevant precursors. In addition, regarding genotoxic (b) (4) indicate if it is detectable and determine the amount of this impurity or its derivatives in the drug substance and relevant precursors.
6. For the degradation product (b) (4), lower the acceptance limit for stability to NMT (b) (4) % (same as release limit) (b) (4).
7. Regarding the drug product container/closure system, confirm that (b) (4), is the supplier of the container/closure (b) (4).
8. Provide the quantitative composition of the (b) (4) material. Alternatively, provide a letter of authorization to a packaging DMF.

9. Provide a diagram of the final shape and size of the drug product container/closure package, or reference an appropriate DMF.
10. Provide a description of how [REDACTED] (b) (4) [REDACTED]. Include a description of the [REDACTED] (b) (4) [REDACTED] and CFR compliance.
11. Provide a description of how the [REDACTED] (b) (4) [REDACTED] integrity is assured at release and throughout the shelf life.
12. Regarding post-approval stability, provide a commitment to put at least one commercial batch on stability per year.
13. Supply draft carton and container labels.

Kindly acknowledge receipt of this email

Regards,  
Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, Bldg 22, Rm 3239  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

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ABOLADE ADEOLU  
04/09/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Monday, March 31, 2014 4:08 PM  
**To:** Pelliccione, Nick (NPelliccione@aezsinc.com)  
**Cc:** Adeolu, Abolade  
**Subject:** NDA 205598

**Importance:** High

Dear Nick,

Submit the following information by April 11, 2014, for NDA 205598 clinical pharmacology review of Study AEZS-130-IIT-1:

- Report any difference in plasma macimorelin concentrations between the first (assay validated October 2003) and second (assay validated July 2005) bioanalytical analyses after oral administration of macimorelin.
- Submit the plasma macimorelin concentration data for the first (assay validated October 2003) bioanalytical analysis.
- Justify the method to assess long-term stability of plasma samples for macimorelin determination after oral and intraduodenal administration during the time period between the first (assay validated October 2003) and second (assay validated July 2005) bioanalytical analyses.
- Define “analyzed directly” in Table IV.1 of Amendment no.2 to the validation report: EP01572: Validated method for the determination of EP01572 in human plasma by HPLC-MS/MS. State the units for the measurement of EP01572 in Table IV.1.
- Submit the validation and bioanalytical report for the determination of plasma growth hormone concentration after oral and intraduodenal administration of macimorelin.

Kindly confirm receipt of this email.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, Bldg 22, Rm 3239  
10903 New Hampshire Avenue,  
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ABOLADE ADEOLU  
03/31/2014

## Adeolu, Abolade

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**From:** Adeolu, Abolade  
**Sent:** Friday, February 28, 2014 10:33 AM  
**To:** Pelliccione, Nick (NPelliccione@aezsinc.com)  
**Cc:** Adeolu, Abolade  
**Subject:** NDA 205598

**Follow Up Flag:** Follow up  
**Flag Status:** Flagged

Dear Nick,

Please see our comments below with regards to the labeling for the macimorelin application

A. Container label

- a. The NDC number is often used as an additional verification method during the drug dispensing process. Therefore, we request you to move NDC number to the top third of the principal display panel per 21 CFR 207.35(3)(iii) to increase the prominence of the NDC number.
- b. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore it is an important safety feature that should be part of the label whenever possible. Your product has not been provided an exception, therefore we request you add the product barcode to each individual pouch as required per 21 CFR 201.25(b)(1)(ii).
- c. Add the statement “For Oral Use Only” to the principal display panel to minimize the risk of wrong route of administration errors.
- d. Add the statement “Must Be Reconstituted Before Use” to the principal display panel to minimize the risk of overdose where the entire pouch dry content is administered as a single dose.
- e. Increase the prominence of strength (e.g. 0.5 mg per mL) to improve readability. f. Include the total drug content statement (e.g. 60 mg per 120 mL, when **APPEARS THIS WAY ON ORIGINAL** reconstituted) on the principal display panel per 21 CFR 201.51 to minimize the risk of overdose where the entire pouch content is administered as a single dose.
- g. Relocate the statement “Directions for use: See enclosed package insert” and the statement “Each pouch contains: (b) (4) mg macimorelin acetate (equivalent to (b) (4) mg macimorelin)” to the back panel as only the most important information such as name of the product and strength should be the most prominent information on the principal display panel.<sup>2</sup>
- h. Re-locate the storage information to the middle section (above the manufacturer information) and revise and bold the statement to “Must be refrigerated, store at 2-8°C (36-46°F).”. We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.
- i. Relocate the manufacturer information to the bottom third of the back panel as it competes for prominence with the storage information.

B. Carton labeling

- a. See section A.a through A.f.

APPEARS THIS WAY ON ORIGINAL

b. As currently presented, the proprietary name and established name competes for prominence with the manufacturer's logo as they all appears to be in the same font size on the principal display panel.

Increase the prominence of the proprietary name and established name by using a larger font size as the current presentation of both proprietary name and established name lack prominence and conspicuousness.

c. Decrease the prominence of the manufacturer's logo on the principal display panel and the back panel by relocating the manufacturer's logo to the bottom third of the principal display panel and back panel as it competes for prominence with the product name. Only the most important information such as name of the product and strength should be the most prominent information on the principal display panel.

d. Relocate the statement "Each pouch contains: (b) (4) mg macimorelin acetate (equivalent to (b) (4) mg macimorelin)" to the back panel as only the most important information such as name of the product and strength should be the most prominent information on the principal display panel.3

e. Revise and bold the storage statement to "Must be refrigerated, store at 2-8°C (36-46°F)". We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

f. Include mixing instructions for reconstituting the product and post-reconstitution expiration date on the back panel if space permits. We acknowledge that this information is available in the Prescribing Information insert, but our post marketing experiences indicate that Prescribing Information insert and container and carton are frequently stored separately during the pharmacy procurement process.

Kindly acknowledge receipt of this email.

Thanks,  
Bola

Bola Adeolu, R.Ph., MS, MBA  
Regulatory Project Manager,  
CDER/OND  
Office of Metabolism and Endocrinology Products  
White Oak, Bldg 22, Rm 3239  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/  
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ABOLADE ADEOLU  
02/28/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA205598

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Aeterna Zentaris GmbH  
c/o Nicholas J. Pelliccione, Ph.D.  
25 Mountainview Boulevard  
100 Marketplace, Suite 203  
Basking Ridge, NJ 07920

ATTENTION: Nicholas J. Pelliccione, Ph.D.  
Sr. Vice President, Regulatory Affairs and Quality

Dear Dr. Pelliccione:

Please refer to your New Drug Application (NDA) dated November 4, 2013, received November 5, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Macimorelin Granules, (b) (4)

We also refer to your November 4, 2013, correspondence, received November 5, 2013, requesting review of your proposed proprietary name, Macrilen. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your November 4, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, M.S., M.B.A., Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Abolade Adeolu, R.Ph., MS, MBA, Regulatory Project Manager, in the Office of New Drugs at (301) 796-4264.

Sincerely,

*{See appended electronic signature page}*

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

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TODD D BRIDGES on behalf of KELLIE A TAYLOR  
01/27/2014



NDA 205598

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

Aeterna Zentaris GmbH  
Attention: Nicholas Pellicione, PhD  
Sr. V.P. Regulatory Affairs and Quality  
100 Marketplace, Suite 203  
Basking Ridge, NJ 07920

Dear Dr. Pellicione:

Please refer to your New Drug Application (NDA) dated November 4, 2013, received November 5, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for macimorelin acetate granules for oral solution.

We also refer to your amendments dated November 12, and 19, 2013.

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**. 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>). Therefore, the user fee goal date is **November 5, 2014**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **July 18, 2014**. In addition, the planned date for our internal mid-cycle review meeting is **April 2, 2014**. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

### **Chemistry Manufacturing and Controls (CMC)**

1. We acknowledge your ongoing effort to identify (b) (4) in the drug substance. Provide the most current summary of studies conducted in this investigation.
2. We acknowledge that you followed our 13-DEC-2011 advice to include an overfill in the drug product packaging (b) (4). However, the NDA does not include information on how the amount of (b) (4) was selected to be an adequate overfill to ensure the target concentration of 0.5 mg/mL macimorelin. Provide a rationale supported by data for the (b) (4) overfill. In addition, explain the impact on efficacy in a situation where the entire content of the (b) (4) including the (b) (4) overfill, can potentially be reconstituted resulting in a higher drug concentration than the target concentration.
3. Confirm that the 60 mg stability batches have the same formulation as the commercial product. Provide a revised table of formulations (e.g., Table 6 in 1.12.15, Table 2 in 2.3.P, Tablet 1 in 3.2.P.2) to include formulations used in clinical studies, stability studies, and commercial product. Revise the percentage quantities of ingredients in the commercial formulation because the current values in the NDA appear to be incorrect.
4. Provide a justification for the omission of Water Content, pH, and Reconstitution Time in the drug product specification.

### **Clinical**

5. Resubmit the Data Tabulation Dataset Legacy, Analysis Dataset Legacy and Analysis Program folders under Module 5, Clinical Study Reports, so that the individual “dataset”, “adam programs”, “derived dataset programs”, “formats”, “macros”, “sdtn programs” and “tlg programs” folders are labeled to describe their individual contents.
6. Given that there were 10 controls who completed the trial at the time of study termination by Ardana Bioscience and you agreed in the SPA to enroll, in addition to the 30 normal control subjects needed to match the number of adult growth hormone deficient (AGHD) patients from the original cohort 20 additional subjects ( 10 AGHD patients and 10 matched normal control subjects). why are there only 48 patients in the control database instead of 50 patients?
7. Since you included 52 AGHD cases in the efficacy data set and only 48 controls why are there no control data for 4 of the AGHD patients? Justify why this should not affect the efficacy analyses.

### **Statistics**

8. Provide subgroup analysis by sex, age and race (and geographic region if applicable) or provide a justification as to why these analyses are not included.

9. We cannot open define.xml file. Provide a corresponding pdf file.
10. Provide copies of the published papers related to the use of your primary measure of diagnostic power and conclusion method.

### **Clinical Pharmacology**

11. In accordance to the food-effect study guidance (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070241.pdf>), provide the content of the “standard liquid meal” used in study ARD-0705-003.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Under Adverse Reactions in Highlights, (b) (4) needs to be removed.
2. Under the Full Prescribing Information section, numbers 15 and 16 in the package insert (PI) should be numbers 16 and 17 respectively.
3. In the ADVERSE REACTIONS section of the PI, use the verbatim statement: “ Because clinical trial are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in practice.”

We request that you resubmit labeling that addresses these issues by **February 14, 2014**. The resubmitted labeling will be used for further labeling discussions.

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

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material

identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

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

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

#### **REQUIRED PEDIATRIC ASSESSMENTS**

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

Because none of these criteria apply to your application, you are exempt from this requirement. If you have any questions, call Abolade (Bola) Adeolu, Regulatory Project Manager, at (301) 796-4264.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, MD  
Director (Acting)  
Division of Metabolism & Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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JEAN-MARC P GUETTIER  
01/15/2014



NDA 205598

**NDA ACKNOWLEDGMENT**

Aeterna Zentaris GmbH  
Attention: Nicholas Pellicione, PhD  
Sr. V.P. Regulatory Affairs and Quality  
100 Marketplace, Suite 203  
Basking Ridge, NJ 07920

Dear Dr. Pellicione:

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: macimorelin acetate granules for oral solution

Date of Application: November 4, 2013

Date of Receipt: November 5, 2013

Our Reference Number: NDA 205598

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 January 4, 2014, in accordance with 21 CFR 314.101(a).

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

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

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

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism & Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

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

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications. If you have any questions, call me at (301) 796-4264.

Sincerely,

*{See appended electronic signature page}*

Abolade (Bola) Adeolu, RPh, MS, MBA  
Regulatory Project Manager  
Division of Metabolism & Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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ABOLADE ADEOLU  
11/12/2013

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



NDA 205598

**LATE-CYCLE MEETING MINUTES**

Biologics Consulting Group, Inc.  
Attention: Kerin Ablashi  
US Agent for Aeterna Zentaris GmbH  
400 N. Washington Street, Suite 100  
Alexandria, VA 22314

Dear Ms. Ablashi:

Please refer to your New Drug Application (NDA) dated November 5, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Macrilen (macimorelin acetate granules) for oral solution.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on July 23, 2014.

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

If you have any questions, call Abolade (Bola) Adeolu, Regulatory Project Manager at (301) 796-4264.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, MD  
Director  
Division of Metabolism & Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** July 23, 2014, from 9:00 to 10:00 AM  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room # 1415  
Silver Spring, MD 20903

**Application Number:** NDA 205598  
**Product Name:** Macrilen (macimorelin acetate granules) for oral solution  
**Applicant Name:** Aeterna Zentaris GmbH

**Meeting Chair:** Jean-Marc Guettier, MD  
**Meeting Recorder:** Abolade (Bola) Adeolu

**FDA ATTENDEES**

Mary Parks, MD - Deputy Director, Office of Drug Evaluation II  
Jean-Marc Guettier, MD – Director, Division of Metabolism & Endocrinology Products (DMEP)  
Dragos Roman, MD - Clinical Team Leader, DMEP  
William Lubas, MD, Clinical Reviewer, DMEP  
David Carlson, PhD - Nonclinical Reviewer, DMEP  
Jeffery Quinn, PhD - Nonclinical Reviewer, DMEP  
Immo Zadezensky, PhD - Clinical Pharmacology Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)  
S.W. Johnny Lau, PhD - Clinical Pharmacology Reviewer, DCPII, OCP  
Thomas Permutt, PhD –Director, Division of Biometrics II  
Lan Huang, PhD - Statistical Reviewer, Division of Biometrics V  
Naomi Redd, PharmD - Risk Management Analyst, Division of Risk Management  
Yelena Maslov, PharmD - Team Leader, Division of Medication Error Prevention and Analysis (DMEPA)  
Mishale Mistry, PharmD – MPH – Safety Evaluator, DMEPA  
Julie Van der Waag, MPH - Chief, Project Management Staff  
Abolade (Bola) Adeolu, RPh, MS, MBA - Regulatory Project Manager

**EASTERN RESEARCH GROUP ATTENDEES**

So Hyun Kim – Independent Assessor

**APPLICANT ATTENDEES**

Richard Sachse, MD, PhD - Chief Scientific Officer / Chief Medical Officer  
Michael Teifel, Ph - Vice President Preclinical Development

Rudi Martens, PhD -Vice President Pharmaceutical Operations

Matthias Gerlach, PhD - Vice President Medicinal Chemistry

Manfred Peukert, PhD -Vice President Medical Affairs

Daniel Croteau, PharmD - Director Medical Affairs

(b) (4) - Consultant Statistician

Jose M. Garcia, MD, PhD - (b) (4) Endocrinologist

Goswin Reuschenbach, PhD - Regulatory Consultant and retired Local Head of Regulatory for  
Aeterna Zentaris

Kerin Ablashi - Biologics Consulting Group, Regulatory

## 1.0 BACKGROUND

NDA 205598 for Macrilen (macimorelin acetate granules) for oral solution as diagnostic for adults growth hormone deficiency was submitted on November 5, 2013.

The Prescription Drug User Fee Act (PDUFA) goal date for the application is November 5, 2014.

FDA issued a Background Package in preparation for this meeting on July 14, 2014.

## 2.0 DISCUSSION

### LCM AGENDA

#### 1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

#### 2. Discussion of Substantive Review Issues – 45 minutes

Each issue will be introduced by FDA and followed by a discussion.

- **Clinical Pharmacology**

- a. *The applicant conducted additional assessments on the plasma macimorelin concentrations after the first and second bioanalytical analyses to demonstrate the stability of macimorelin in their more than 10 months storage of plasma samples. They noted that the mean deviation in the repeated plasma macimorelin concentrations of 2% suggests that the samples were stable during storage. The Agency disagreed stating that analyzing the samples a second time after more than 10 months storage did not prove stability because the results may be confounded with factors such as variability of the 2 analyses. The proper way to show stability is to add storage samples with known macimorelin concentrations to the samples of unknown macimorelin concentrations and to compare the results after long-term storage. The Agency pointed out that even though the mean deviation between the first and second analyses averaged to 2.08% the range in*

*the samples was quite large -36.92 to 49.92. If the pharmacokinetic data from Study AEZS-130-IIT is deemed necessary for labeling, the applicant will need to repeat the analysis with seeded samples of known concentrations stored for the same length of time and under the same conditions as the clinical unknown samples to establish the stability of macimorelin in plasma samples.*

- b. The applicant claimed that they had retrieved documents that can show the validation of the bioanalytical assay for measuring serum growth hormone concentrations from the hospital in (b) (4) that they conducted Study AEZS-130-IIT. Those documents were written in German. The applicant agreed to submit the documents along with an English translation.*
- c. The applicant claimed that serum samples for the measurement of growth hormone for all patients were available from Study AEZS-130-047. The applicant also claimed that there was a mistake in the bioanalytical report (VR07-(b) (4)-018) when it stated that the serum samples were not available due to a protocol deviation for Visit 2 from 4 subjects and that instead backup plasma samples had been used to replace the missing serum samples for growth hormone measurement. The Agency asked the applicant to specifically confirm that the growth hormone concentration measurement for Subject 0609 was indeed determined from serum samples.*

*The Agency reminded the applicant to carefully document their claims for the above issues.*

- **Statistics**

*The Agency emphasized that the applicant missed the primary endpoint which had been agreed upon in the SPA and stated that Per Protocol (PP) analyses were considered exploratory.*

*The applicant emphasized that for a diagnostic test a Per Protocol analysis is preferred as the results would more likely be applicable to distinguishing true cases from controls. Therefore, they believe that their PP analysis which did meet the prespecified threshold of a lower bound of 0.85 for ROC AUC at the 99%CI is relevant.*

*The Agency mentioned while it is true that for a diagnostic test it is optimal for the analysis to be performed on true cases and true controls that it did not appear that the two subjects the applicant chose to withdraw from their PP analysis namely, 0608 and 0609, did in fact improve the dataset. According to the case report form (CRF) subject 0609 was excluded because she did not have a low IGF-1 level, but the Agency noted that the CRF showed she had multiple low IGF-1 levels. The applicant stated that the CRF was wrong and that the patient was actually excluded because she only had one confirmed pituitary hormone deficiency even though she was getting three different hormone replacement therapies. The applicant stated that while they had still not been able to get the original site data for this patient they had contacted the investigator who had access to some source information and they would submit that information to help clarify why this patient should have been excluded from the study. The Agency then asked if the applicant really wanted to only include patients with GH deficiencies in the case group and controls in the control group why they proposed to exclude patient 0608 from the case group*

*when all the GH stimulation tests showed this patient did have GH deficiency and why they kept subject 0307 in the case group when the prestudy GH testing showed that this subject did not have GH deficiency. The applicant acknowledged these inconsistencies.*

*The Agency concluded that had the applicant appropriately enrolled cases and controls that the final study results for the primary endpoint could have been different but that the reason the Agency requires an ITT analysis is to avoid such post hoc analyses.*

*The Agency mentioned there is a significant imbalance in the term “Race” between the AGHD group and the matched control group. The applicant acknowledged this and stated that it had occurred because “Race” was not included in the matching criteria for the case-control study. However, they did not believe there was scientific evidence to support “Race” as a related risk factor and their statistical models showed that “Race” is not a significant factor in their models. The Agency stated that because the sample size for African Americans is very small it is not possible to draw any clear conclusions about efficacy in this population.*

*The Agency mentioned there is a significant imbalance in study site between the AGHD group and the matched control group. The applicant stated that they believed that “Site” is not a risk factor and the reality was that the individual characteristics of the study sites made it difficult to enroll both cases and controls for some sites. The Agency argued that the different features at each site (i.e. access to different patient populations, geographical locations, clinical expertise etc.) may have confounded the test results.*

*The Agency mentioned that given the test results the determination of the optimal cut-point is a challenge. The applicant argued that the optimal cut-point did vary depending on the final analysis, but the performance of the test is reasonable within a range of cut-point values. The Agency asked the applicant if a range of cut-points might be more useful for a clinician. The Agency was concerned that the results using cut-points obtained from one dataset may not be reproduced in another dataset. The pre-specified cut-point 8.5 ng/mL (obtained from studies in the literature and pre-specified by the sponsor) performed poorly in terms of sensitivity and specificity in this study. The performance is also inconsistent between the previously enrolled and newly enrolled subjects. The Agency believes it is necessary to show that the cut-points selected from this study are effective in another confirmative study. The applicant acknowledged the issue of reproducibility.*

*The Agency pointed out that there has been multiple communications between the Agency and applicant regarding the statistical plan and that the Agency agreed to the proposed plan in the SPA.*

## **• Clinical**

*The Agency asked if the applicant was able to identify source data confirming the inclusion criteria for three of the ten newly enrolled cases (0627, 0628 and 0629) that were to be evaluated as part of a secondary endpoint in the SPA analysis. This information was missing along with information on the criteria used for diagnosis of GH deficiency on a total of 13 cases in the last table the applicant had submitted on July 3, 2014, in response to a prior information*

request. The applicant stated they had recently acquired information on these three patients and on some but not all of the other 13 cases mentioned, and they would submit the new information to the agency.

The Agency stated that critical information in the submission and in some of the CRFs was in error. The fact that such incorrect data or missing information could be corrected after the Agency's data inquiries, raised questions of the integrity of the rest of the data. As additional examples the clinical reviewer mentioned that the inspections at two of the study sites came back with "inaccurate record keeping" and "record issues". The ECGs from subject 0930 which had all been taken within a two hour period had the machine recorded times altered. The applicant's own table summarizing time schedule and procedural deviations (Table 14.1.4) identified problems with 57% of cases and 73% of controls. This impacts the reliability of basing the test result on a single GH measurement at 45 minutes, rather than using the all of the observed measurements between 30 and 60 minutes. Applicant acknowledged deficits in record keeping but that monitoring visits were made and documented.

The Agency stated that the type and degree of inconsistencies seen with the data sources are out of the ordinary.

The applicant was asked to explain why the macimorelin data for subject 0930 which showed a typical decline from C<sub>max</sub> at 0.75 hrs to the 2 hour time point should show a rebound in macimorelin levels almost back up to C<sub>max</sub> at the 2.5 hour time point. The applicant was not able to explain this but insisted it was not likely to be due to the mix up in samples as this was the only subject studied at the clinical site at the time.

The applicant was asked how convinced they were that macimorelin was responsible for the QT prolongation seen in the single patient 0930 given that he was on two other drugs that can prolong QT and that the peak in macimorelin concentration appeared to occur several hours before the peak in QT<sub>c</sub>. The applicant stated they were not sure but they believed that they did not need to do a thorough QT<sub>c</sub> study to clarify this point given that the drug would be given as a single one time dose.

In response to a question from the Agency, the applicant acknowledged that they were studying macimorelin (b) (4) with repeat dosing but that they were being followed closely for QT<sub>c</sub> prolongation with repeat ECGs.

### 3. Review Plans – 5 minutes

Internal Wrap-up Meeting: September 15, 2014

### 4. Wrap-up and Action Items – 5 minutes

Applicant was asked to submit responses and additional data as requested

***This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.***

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/s/  
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JEAN-MARC P GUETTIER  
08/14/2014



NDA 205598

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Biologics Consulting Group, Inc.  
Attention: Kerin Ablashi  
US Agent for Aeterna Zentaris GmbH  
400 N. Washington Street, Suite 100  
Alexandria, VA 22314

Dear Ms. Ablashi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Macrilen (macimorelin acetate granules) for oral solution.

We also refer to the Late-Cycle Meeting (LCM) scheduled for July 23, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Abolade (Bola) Adeolu, Regulatory Project Manager, at (301) 796-4264.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, MD  
Director  
Division of Metabolism & Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
Late-Cycle Meeting Background Package

## **LATE-CYCLE MEETING BACKGROUND PACKAGE**

**Meeting Date and Time:** July 23, 2014, from 9:00 to 10:00 AM  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22; Conference Room # 1415  
Silver Spring, MD 20903

**Application Number:** NDA 205598  
**Product Name:** Macrilen (macimorelin acetate granules) for oral solution  
**Indication:** Diagnostic for adults growth hormone deficiency  
**Sponsor/Applicant Name:** Aeterna Zentaris GmbH

### **INTRODUCTION**

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

### **BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE**

#### **1. Discipline Review Letters**

No Discipline Review letters have been issued to date.

#### **2. Substantive Review Issues**

**SUBSTANTIVE REVIEW ISSUES HAVE BEEN IDENTIFIED AND ARE UNRESOLVED**

The following substantive review issues have been identified to date:

### **Clinical Pharmacology**

Plasma samples were measured twice for macimorelin concentration in Study AEZS-130-IIT-1. You only reported the second macimorelin measurement. A lapse of more than 10 months exists between the 2 measurements. Thus, stability of macimorelin in the plasma samples under storage is questionable. Your substantiation for the stability of the plasma samples under storage as submitted on April 11, 2014, for Study AEZS-130-IIT-1 is not acceptable. Also, there are no validation report and bioanalytical report for the measurement of growth hormone in serum samples for Study AEZS-130-IIT-1.

Without acceptable plasma macimorelin concentration and serum growth hormone concentration data for Study AEZS-130-IIT-1, the following data will be unacceptable:

- macimorelin pharmacokinetic dose proportionality data
- macimorelin exposure-response data
- macimorelin dose-response data
- optimal macimorelin dose data

The substantiation to use lithium-heparinized plasma pharmacokinetic backup samples to substitute for the missed serum samples of Study AEZS-130-047 on Visit 2 for 4 subjects per Report VR07-(b) (4)-018 is not acceptable due to the wide range of the percent difference between plasma growth hormone concentration and serum growth hormone concentration for the tested samples. Thus, the reported serum growth hormone concentration results on Visit 2 for 4 subjects of Study AEZS-130-047 are not reliable.

### **Statistics**

Statistical significance was not achieved in the pre-planned primary analysis of the study. For the pre-planned primary analysis, the lower bound of the 99% confidence interval for the ROC AUC is <0.85, the pre-specified threshold.

There is a significant imbalance in race between the adult GH deficiency (AGHD) group and the matched control group. Two of 52 AGHD patients (4%) and 18 out of 48 matched controls (38%) are black or African American. Race may be a confounding factor in the evaluation of the diagnostic efficacy of your product.

There is a significant imbalance in study site between the AGHD group and the matched control group. For example, no AGHD patients were enrolled from Sites 11 and 17, and most of the matched controls were enrolled from Sites 09, 10, 11 and 17. Site may be a confounding factor in the evaluation of the diagnostic efficacy of your product.

The determination of the optimal cut-point is a challenge. Different approaches may lead to different cut-points. In addition, the selected cut-point was based on the same data that was used to determine its sensitivity and specificity. Therefore, the estimates of sensitivity and specificity

may overstate the truth. It is not clear if the sensitivity and specificity obtained in Study AEZS-130-047 can be reproduced in another study.

For both sensitivity and specificity, using the 8.5 cut-point (pre-specified in the protocol) and the 2.7 cut-point (optimal cut-point determined from the data), the performance for the newly enrolled patients is worse than the previously enrolled subjects. The results are not consistent (previously vs. newly enrolled).

It is not clear if the matched control group includes subjects belonging to the intended patient population, who would seek diagnosis of possible AGHD and would benefit from the test. The performance (ROC AUC, sensitivity and specificity) of macimorelin for the intended patient population is not known.

### **Clinical**

We are concerned that there are 14 subjects out of the 52 cases of AGHD with insufficient evidence to support their inclusion as cases in the current study.

Subject 307 did not have GHD according to the current guidelines for the arginine test, nor did the patient have evidence of GHD by the L-ARG + GHRH test performed during the study.

Subject 609 did not have a pretrial test to support GHD and the L-ARG + GHRH test performed during the study suggests the patient does not have GHD. In addition the only macimorelin data on this patient was performed using plasma samples which are not reliable.

Subjects 627, 628 and 629 have no data to support that these patients have GHD.

Subjects 603, 604, 608, 611, 701, 702 703 801 and 802 have no pretrial data to support a diagnosis of GHD. Only data from an L-ARG + GHRH test performed during the study suggest that these patients might have GHD.

The efficacy results obtained from poor quality data may not be reliable.

Poor record keeping by the original sponsor, Ardana, such as not keeping adequate records of baseline data to confirm inclusion criteria for subjects enrolled in the trial and possibly other site specific data, is in violation of Good Clinical Practice standards (refer to the April 1996 FDA Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance at <http://www.fda.gov/downloads/Drugs/Guidance/ucm073122.pdf>).

Given that macimorelin can act at both the hypothalamus and pituitary to promote GH release clarify if it is possible that a lesion confined to the hypothalamus could still be associated with normal levels of stimulated GH following macimorelin administration. In addition, provide information as to whether a hypothalamic lesion would typically be expected to lead to atrophy of the somatotroph and subsequent lack of response to macimorelin, and provide any information you have regarding the time course of such atrophy.

**ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned

**REMS OR OTHER RISK MANAGEMENT ACTIONS**

No issues related to risk management have been identified at this time.

**LCM AGENDA**

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 45 minutes

Each issue will be introduced by FDA and followed by a discussion.

- Clinical Pharmacology
- Statistics
- Clinical

3. Review Plans – 5 minutes

Wrap up meeting: September 15, 2014

4. Wrap-up and Action Items – 5 minutes

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/s/  
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JEAN-MARC P GUETTIER  
07/14/2014