

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209899Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

## RECOMMENDATION

|  |
|--|
| <input checked="" type="checkbox"/> Approval                     |
| <input type="checkbox"/> Approval with Post-Marketing Commitment |
| <input type="checkbox"/> Complete Response                       |

### NDA 209899 Resubmission 13 Assessment #1

|                                |                            |
|--------------------------------|----------------------------|
| <b>Drug Product Name</b>       | Ozanimod Capsules          |
| <b>Dosage Form</b>             | Immediate Release Capsules |
| <b>Strength</b>                | 0.23 mg, 0.46 mg, 0.92 mg  |
| <b>Route of Administration</b> | Oral                       |
| <b>Rx/OTC Dispensed</b>        | Rx                         |
| <b>Applicant</b>               | Celgene Corporation        |
| <b>US agent, if applicable</b> | n/a                        |

| Submission(s)        | Document Date | Submission(s)     | Document Date            |
|----------------------|---------------|-------------------|--------------------------|
| Resubmission (SD 13) | 25-MAR-2019   | Amendment (SD 24) | 23-JUL-2019              |
| Amendment (SD17)     | 06-MAY-2019   | Amendment (SD 29) | 19-SEP-2019              |
| Amendment (SD 19)    | 14-JUN-2019   | Amendment (SD 35) | 30-OCT-2019              |
| Amendment (SD 23)    | 22-JUL-2019   | Amendment (SD XX) | Email Responses Dec 2019 |

#### QUALITY ASSESSMENT TEAM

| Discipline                                 | Primary Assessment | Secondary Assessment     |
|--|--------------------|--------------------------|
| <b>Drug Substance</b>                      | Rajan Pragani      | Suong Tran               |
| <b>Drug Product</b>                        | Grace Chiou        | Wendy Wilson-Lee         |
| <b>Manufacturing</b>                       | Yuesheng Ye        | Nallaperumal Chidambaram |
| <b>Biopharmaceutics</b>                    | Qi Zhang           | Ta-Chen Wu               |
| <b>Regulatory Business Process Manager</b> | Dahlia Walters     |                          |
| <b>Application Technical Lead</b>          | Wendy Wilson-Lee   |                          |

# EXECUTIVE SUMMARY

## I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

OPQ recommends **APPROVAL** of NDA 209899 for commercialization of with an expiration dating period of 24 months for the 0.23 mg drug product and 36 months for the 0.46 mg and 0.92 mg capsules when stored at controlled room temperature:

- The applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product.
- The Office of Pro Manufacturing Assessment made a recommendation of approval for all the facilities involved in this application.
- The proposed labeling and labels have adequate information to meet the regulatory requirements.

## II. SUMMARY OF QUALITY ASSESSMENTS

### A. Product Overview

Celgene seeks approval of ozanimod capsules for the treatment of relapsing forms of multiple sclerosis. Ozanimod is a new molecular entity (NME); however, no regulatory designations such as orphan or breakthrough were granted for this product. The proposed recommended daily dose is 0.92 mg after titration using a 0.23 mg daily dose followed by a 0.46 mg daily dose. The application was originally submitted December 2017 but filing issues were identified related to nonclinical and clinical pharmacology. A refuse to file letter was issued February 2018.

OPQ provided advice on the CMC development program via an End of Phase 2 CMC meeting (March 2014) and two, Type C Written Responses CMC meetings (May 2016, May 2017). Additional guidance was provided in response to email inquiries from the sponsor regarding the drug substance stability package (May 2017). Topics of discussion included number of drug substance batches required for registration; designation of starting materials; quality control of starting materials, intermediates, final drug substance, and drug product; characterization and qualification of drug substance impurities; validation activities; registration stability program for the drug substance and drug product; and dissolution method development. Celgene submitted a BCS Class 1 designation request for ozanimod capsules; however, the FDA BCS Committee denied the request (Advice Letter dated June 2017).

Based on the initial risk assessment, content uniformity and particle size were identified as high-

risk attributes (b) (4). Other key review issues included characterization and control of the NME drug substance, the necessity and suitability of the proposed (b) (4) blister packs for the drug product, and bridging the proposed commercial formulation and process to that used for the pivotal clinical studies.

|   |  |
|---|--|
| <b>Proposed Indication(s) including Intended Patient Population</b> | For the treatment of adults with relapsing forms of multiple sclerosis |
| <b>Duration of Treatment</b>  | Chronic  |
| <b>Maximum Daily Dose</b>   | 0.92 mg (proposed)   |
| <b>Alternative Methods of Administration</b>                        | None   |

## B. Quality Assessment Overview

### Drug Substance:

This review covers the drug substance ozanimod hydrochloride. Upon review of the information, no significant quality issues were encountered. (b) (4) have both been selected as commercial suppliers. (b) (4) provided the drug substance for batches in pivotal clinical studies. Several batches using comparable commercial processes B and C have been made at each facility and support comparability between the two suppliers.

The drug substance is soluble at pH 1-7.5 (1 mg/250 mL). The manufacturing process (b) (4) (b) (4). The drug substance is chiral (S-configuration). Chirality, polymorphic form, and particle size (d90 only for the highly soluble drug) are monitored in the drug substance specification. Approach to impurity control (organic, elemental, residual solvent, and potential mutagenic impurities) is acceptable. Potential mutagenic impurities were assessed via QSAR, the analysis was consistent with structural features, and adequately addressed mutagenic risk. The starting materials (b) (4) are at reasonable points in the synthesis and are in line with ICH Q11.

Based on the stability data provided for the registration batches, a proposed retest date of (b) (4) months (room temperature) is acceptable for ozanimod hydrochloride.

### Drug Product:

The drug product is an immediate release drug product available in strengths of 0.23 mg, 0.46 mg, and 0.92 mg of ozanimod (0.25 mg, 0.5 mg and 1.0 mg of ozanimod hydrochloride). Different colored hard gelatin capsules are filled with the appropriate drug product strength formulation (b) (4) (b) (4). The drug product is to be packaged in blister packs or HDPE bottles. The drug product is to be stored at controlled room temperature. Celgene has proposed a 24-month shelf life for the 0.23 mg drug product and a 36-month shelf life for the 0.46 mg and 0.92 mg capsules which are all acceptable.

### **Labeling:**

Recommended revisions to labeling were communicated to the clinical division and applicant. Labeling, including the prescribing information, carton and container labels, and structured product label elements will be adequate once the recommended revisions are accepted and implemented.

### **Manufacturing:**

The manufacturing process includes (b) (4).  
(b) (4).  
The product contains (b) (4).  
(b) (4). The initial application only included (b) (4).  
(b) (4) but was revised after information requests to include controls (b) (4).  
(b) (4).

The applicant developed three manufacturing processes for this drug product: Process 1, Process 2 and Process 3. The intended commercial manufacturing process is Process 3 and is the same at both drug product manufacturing facilities. The statement of no overage and no reprocessing was provided. However, the applicant reported that fill weight overage (i.e., overfill) was used (b) (4) when Process 2 was used. An overfill will not be used for the intended commercial process but fill weight should be confirmed for any future manufacturing process changes post-approval. The applicant provided master batch records (MBRs) in the regional section.

### **Biopharmaceutics:**

This Biopharmaceutics review focuses on 1) the evaluation of the adequacy of the proposed dissolution method and acceptance criterion, and 2) formulation/drug product bridging throughout product development. The proposed dissolution method [500 ml of 0.01 N HCl using USP Apparatus 1 (basket) at 100 rpm] and acceptance criterion [NLT (b) (4)% (Q) in 15 minutes] for the proposed drug product batch release and stability testing are acceptable. The dissolution risk is deemed low, based on the totality of information and data provided (b) (4).  
(b) (4)

The proposed commercial and clinical formulations are different with regard to (b) (4).  
(b) (4). In addition, there are changes in manufacturing process and manufacturing site between the commercial and clinical drug products. The Applicant demonstrated the similarity in the dissolution profiles using different pH media (0.01N HCl, USP pH 1.2 buffer, pH 4.5 acetate buffer, FeSSIF (pH 5.0), and FaSSIF (pH 6.5)) to establish the bridging between the clinical and commercial batches. The product bridging is deemed adequate.

**C. Risk Assessment**

| From Initial Risk Identification |  |                      | Assessment               |                       |                          |
|----------------------------------|--|----------------------|--------------------------|-----------------------|--------------------------|
| Critical Quality Attribute       | Factors that can impact the CQA  | Initial Risk Ranking | Risk Mitigation Approach | Final Risk Evaluation | Lifecycle Considerations |
| Assay                            | Formulation<br>Container closure<br>Raw materials<br>Process<br>Scale<br>Equipment<br>Site | Low                  |                          | Acceptable            |                          |
| Solid State                      |  | Low                  |                          | Acceptable            |                          |
| Content Uniformity               |  | High                 | (b) (4)                  | Acceptable            | (b) (4)                  |
| Microbial Limits                 |  | Low                  |                          | Acceptable            |                          |
| Dissolution                      |  | Low                  |                          | Acceptable            |                          |
| Water Content                    |  | Low                  |                          | Acceptable            |                          |
| Particle Size                    |  | High                 | (b) (4)                  | Acceptable            | (b) (4)                  |

**D. List of Deficiencies for Complete Response**

None.

*Application Technical Lead Name and Date:*

# QUALITY ASSESSMENT DATA SHEET

## 1. RELATED/SUPPORTING DOCUMENTS

### A. DMFs:

See Drug Product Review, Section P.7 Container Closure

### B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

| Document | Application Number | Description  |
|----------|--------------------|--|
| IND      | 109159             | Ozanimod Capsules (RPC1063) for multiple sclerosis |
| IND      |                    |  |
| IND      |                    |  |

(b) (4)

## 2. CONSULTS

None.



Wendy  
Wilson- Lee

Digitally signed by Wendy Wilson- Lee  
Date: 12/10/2019 03:17:12PM  
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## CHAPTER IV: LABELING

### [IQA NDA Assessment Guide Reference](#)

#### 1.0 PRESCRIBING INFORMATION

**Assessment of Product Quality Related Aspects of the Prescribing Information: The PI assessed in this review was submitted on 13August2019. Based on the information provided, there are minor edits to be made to the labeling portion of this submission.**

#### 1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

| Item  | Information Provided in the NDA          | Assessor's Comments   |
|---|--|---|
| <b>Product Title in Highlights</b>  |  |   |
| Proprietary name  | Zeposia (ozanimod) capsules for oral use | Adequate<br>Revise to include a comma before "for oral use" |
| Established name(s)   |  |   |
| Route(s) of administration  |  |   |
| <b>Dosage Forms and Strengths Heading in Highlights</b>   |  |   |
| Summary of the dosage form(s) and strength(s) in metric system.   | Capsules: 0.23 mg, 0.46 mg, and 0.93 mg  | Adequate  |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"   | NA                                       | NA  |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package. | NA                                       | NA  |

## 1.2 FULL PRESCRIBING INFORMATION

### 1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

| Item  | Information Provided in the NDA | Assessor's Comments |
|---|---------------------------------|---------------------|
| <b>DOSAGE AND ADMINISTRATION section</b>  |                                 |                     |
| Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product) | NA                              | NA                  |

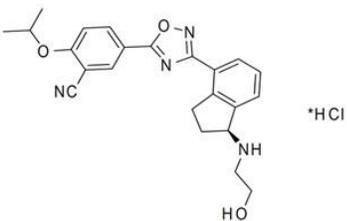
### 1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

| Item   | Information Provided in the NDA  | Assessor's Comments |
|--|--|---------------------|
| <b>DOSAGE FORMS AND STRENGTHS section</b>  |  |                     |
| Available dosage form(s)   | ZEPOSIA is available as capsules in the following dosage strengths:  | <i>Adequate</i>     |
| Strength(s) in metric system   | <ul style="list-style-type: none"> <li>Ozanimod 0.23 mg (b) (4): light grey opaque body/light grey opaque cap imprinted with black ink "OZA" on the cap and "0.23 mg" on the body</li> </ul> |                     |
| If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance   | <ul style="list-style-type: none"> <li>Ozanimod 0.46 mg (b) (4): light grey opaque body/orange opaque cap imprinted with black ink "OZA" on the cap and "0.46 mg" on the body</li> </ul>     |                     |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting   | <ul style="list-style-type: none"> <li>Ozanimod 0.92 mg (b) (4): orange opaque body/orange opaque cap imprinted with black ink "OZA" on the cap and "0.92 mg" on the body</li> </ul>         |                     |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"  | NA   | NA                  |
| For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package. | NA   | NA                  |

### 1.2.3 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

| Item  | Information Provided in the NDA  | Assessor's Comments  |
|---|--|--|
| <b>DESCRIPTION section</b>  |  |  |
| Proprietary and established name(s)   | (b) (4)  | Adequate   |
| Dosage form(s) and route(s) of administration<br>If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.                                  | Ozanimod capsules are provided as hard gelatin (b) (4) capsules for oral administration, containing 0.23, 0.46, or 0.92 mg of ozanimod, equivalent to 0.25, 0.5, and 1 mg ozanimod HCl, respectively.  | Adequate   |
| List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.  | The ozanimod capsules consist of the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The capsule shell, imprinted with black ink, contains the following inactive ingredients: gelatin, titanium dioxide, yellow iron oxide, red iron oxide, and black iron oxide. | <i>Inadequate: Revise to ensure all items are in alphabetical order.</i> |
| For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. | NA   | NA   |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol  | NA   | NA   |
| Statement of being sterile (if applicable)  | NA   | NA   |
| Pharmacological/therapeutic class   | (b) (4)  | Adequate   |

|   |   |                 |
|---|---|-----------------|
| <p>Chemical name, structural formula, molecular weight</p> <p>Other important chemical or physical properties (such as pKa or pH)</p> | <p>The chemical name of ozanimod HCl is 5-(3-((1S)-1-[(2-hydroxyethyl)amino]-2,3-dihydro-1H-inden-4-yl)-1,2,4-oxadiazol-5-yl)-2-[(propan-2-yl)oxy]benzotrile, monohydrochloride.</p> <p>Ozanimod HCl is a white to off-white solid that is freely soluble in water and alcohol with a molecular weight (b) (4) of 440.92.</p> <p>The chemical structure is:</p>  | <p>Adequate</p> |
| <p>If radioactive, statement of important nuclear characteristics.</p>  | <p>NA</p>   | <p>NA</p>       |

### Section 11 (DESCRIPTION) Continued

| Item   | Information Provided in the NDA   | Assessor's Comments |
|--|-----------------------------------|---------------------|
| <p>For oral prescription drug products, include gluten statement if applicable</p>   | <p>NA</p>                         | <p>NA</p>           |
| <p>Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")</p> | <p>No promotional statements.</p> | <p>Adequate</p>     |

### 1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

| Item  | Information Provided in the NDA   | Assessor's Comments   |                 |            |               |         |              |                    |   |              |             |   |              |  |   |                  |  |  |                  |          |
|---|---|-----------------------|-----------------|------------|---------------|---------|--------------|--------------------|---|--------------|-------------|---|--------------|--|---|------------------|--|--|------------------|----------|
| <b>HOW SUPPLIED/STORAGE AND HANDLING section</b>  |   |                       |                 |            |               |         |              |                    |   |              |             |   |              |  |   |                  |  |  |                  |          |
| Available dosage form(s)  | ZEPOSIA is available as capsules in the following dosage strengths:   | Adequate              |                 |            |               |         |              |                    |   |              |             |   |              |  |   |                  |  |  |                  |          |
| Strength(s) in metric system  | <ul style="list-style-type: none"> <li>• Ozanimod 0.23 mg (b) (4)<br/>(b) (4): light grey opaque body/light grey opaque cap imprinted with black ink "OZA" on the cap and "0.23 mg" on the body</li> <li>• Ozanimod 0.46 mg (b) (4)<br/>(b) (4) light grey opaque body/orange opaque cap imprinted with black ink "OZA" on the cap and "0.46 mg" on the body</li> <li>• Ozanimod 0.92 mg (b) (4)<br/>(b) (4) orange opaque body/orange opaque cap imprinted with black ink "OZA" on the cap and "0.92 mg" on the body</li> </ul>  | Adequate              |                 |            |               |         |              |                    |   |              |             |   |              |  |   |                  |  |  |                  |          |
| Available units (e.g., bottles of 100 tablets)  | <table border="1" data-bbox="574 978 1235 1260"> <thead> <tr> <th>Package configuration</th> <th>Tablet strength</th> <th>NDC number</th> </tr> </thead> <tbody> <tr> <td>Bottles of 30</td> <td>0.92 mg</td> <td>59572-820-30</td> </tr> <tr> <td>7-Day Starter Pack</td> <td>7-capsule starter pack containing (4) 0.23 mg capsules and (3) 0.46 mg capsules</td> <td>59572-810-07</td> </tr> <tr> <td>Starter Kit</td> <td>37-capsule starter kit including: a 7-capsule starter pack containing (4) 0.23 mg capsules and (3) 0.46 mg capsules and</td> <td>59572-890-91</td> </tr> <tr> <td>(7-Day Starter Pack + 0.92 mg 30 count Bottle)</td> <td>a bottle containing (30) 0.92 mg capsules</td> <td>59572-(b) (4)-07</td> </tr> <tr> <td></td> <td></td> <td>59572-(b) (4)-30</td> </tr> </tbody> </table> | Package configuration | Tablet strength | NDC number | Bottles of 30 | 0.92 mg | 59572-820-30 | 7-Day Starter Pack | 7-capsule starter pack containing (4) 0.23 mg capsules and (3) 0.46 mg capsules | 59572-810-07 | Starter Kit | 37-capsule starter kit including: a 7-capsule starter pack containing (4) 0.23 mg capsules and (3) 0.46 mg capsules and | 59572-890-91 | (7-Day Starter Pack + 0.92 mg 30 count Bottle) | a bottle containing (30) 0.92 mg capsules | 59572-(b) (4)-07 |  |  | 59572-(b) (4)-30 | Adequate |
| Package configuration   | Tablet strength   | NDC number            |                 |            |               |         |              |                    |   |              |             |   |              |  |   |                  |  |  |                  |          |
| Bottles of 30   | 0.92 mg   | 59572-820-30          |                 |            |               |         |              |                    |   |              |             |   |              |  |   |                  |  |  |                  |          |
| 7-Day Starter Pack  | 7-capsule starter pack containing (4) 0.23 mg capsules and (3) 0.46 mg capsules   | 59572-810-07          |                 |            |               |         |              |                    |   |              |             |   |              |  |   |                  |  |  |                  |          |
| Starter Kit   | 37-capsule starter kit including: a 7-capsule starter pack containing (4) 0.23 mg capsules and (3) 0.46 mg capsules and   | 59572-890-91          |                 |            |               |         |              |                    |   |              |             |   |              |  |   |                  |  |  |                  |          |
| (7-Day Starter Pack + 0.92 mg 30 count Bottle)  | a bottle containing (30) 0.92 mg capsules   | 59572-(b) (4)-07      |                 |            |               |         |              |                    |   |              |             |   |              |  |   |                  |  |  |                  |          |
|   |   | 59572-(b) (4)-30      |                 |            |               |         |              |                    |   |              |             |   |              |  |   |                  |  |  |                  |          |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"   | NA  | NA                    |                 |            |               |         |              |                    |   |              |             |   |              |  |   |                  |  |  |                  |          |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package. | NA  | NA                    |                 |            |               |         |              |                    |   |              |             |   |              |  |   |                  |  |  |                  |          |

**Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)**

| Item   | Information Provided in the NDA   | Assessor's Comments  |
|--|---|--|
| Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)                           | NA  | NA   |
| If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."   | NA  | NA   |
| Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.   | Store at 20°C - 25°C (68°F - 77°F); excursions permitted between 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature]. | <i>Inadequate<br/>Replace "-" with "to" to avoid confusion with minus sign</i> |
| Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free." | NA  | NA   |
| Include information about child-resistant packaging  | No information included.  | Adequate   |

**1.2.5 Other Sections of Labeling**

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

### 1.2.6 Manufacturing Information After Section 17 (for drug products)

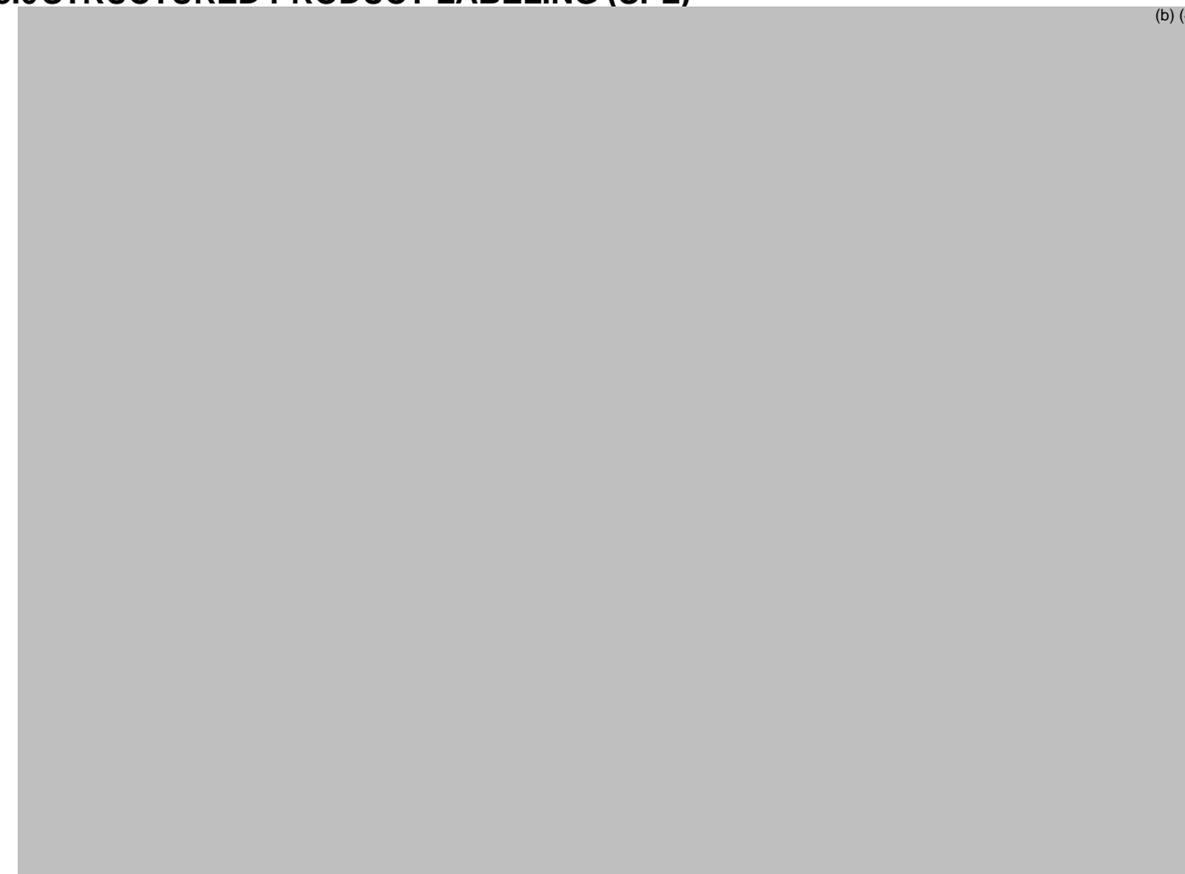
| Item   | Information Provided in the NDA                              | Assessor's Comments  |
|--|--|--|
| <b>Manufacturing Information After Section 17</b>  |  |  |
| Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer | Manufactured for:<br>Celgene Corporation<br>Summit, NJ 07901 | <i>Inadequate: Revise to include street address per 21 CFR 201.1 (i)</i> |

## 2.0 PATIENT LABELING

**Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): NA**

## 3.0 STRUCTURED PRODUCT LABELING (SPL)

(b) (4)



**Reviewer's Assessment of SPL: *Adequate***

## **4.0 CARTON AND CONTAINER LABELING**

### **4.1 Container Label**

- a. Label for 30 count of 0.92 mg capsule

| Item   | Information Provided in the NDA   | Assessor's Comments about Carton Labeling   |
|--|---|---|
| Proprietary name, established name, and dosage form (font size and prominence)         | ZEPOSIA (ozanimod) capsules   | Adequate  |
| Dosage strength  | 0.23 mg, 0.46 mg, 0.92 mg   | Adequate  |
| Route of administration  | Orally once daily   | Adequate; listed on carton for kits only. As this is an oral drug, this is acceptable |
| If the active ingredient is a salt, include the equivalency statement per FDA Guidance | <p>Each 0.23 mg capsule contains 0.23 mg ozanimod (equivalent to 0.25 mg ozanimod hydrochloride).</p> <p>Each 0.46 mg capsule contains 0.46 mg ozanimod (equivalent to 0.5 mg ozanimod hydrochloride).</p> <p>Each 0.92 mg capsule contains: 0.92 mg (equivalent to 1 mg ozanimod hydrochloride).</p> | Adequate  |
| Net contents (e.g. tablet count)   | Starter kit says : 37 capsules  | Adequate  |
| "Rx only" displayed on the principal display   | "Rx only" displayed   | Adequate  |

|  |  |  |
|--|--|--|
| NDC number   | <p>7-day starter pack sold individually:<br/>NDC 59572-810-07<br/>0.92 mg capsule bottle sold individually:<br/>NDC 59572-820-30</p> <p>Commercial starter kit:<br/>NDC 59572-890-91 (starter kit)<br/>NDC 59572-(b) (4)-07 (7-day starter pack)<br/>NDC 59572-(b) (4)-30 (0.92 mg 30 count bottle)</p> <p>Sample (b) (4) kit:<br/>NDC 59572-890-97 (b) (4)<br/>NDC 59572-(b) (4) 97 (7-day (b) (4) pack)<br/>NDC 59572-820-97 (0.92 mg 30 count bottle)</p> | Adequate   |
| Lot number and expiration date   |  <p>LOT 12345<br/>EXP MMYYYY<br/>SN 1234567890<br/>GTIN 1234567890</p>   | Adequate   |
| Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.                                       | Store at 20°C - 25°C (68°F - 77°F); excursions permitted between 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature].  | <i>Inadequate</i><br><i>Replace “-” with “to” to avoid confusion with minus sign</i> |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use) | NA   | NA   |
| Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.                      | NA   | NA   |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol   | NA   | NA   |
| Bar code   | Present  | Adequate   |

| Item  | Information Provided in the NDA          | Assessor's Comments about Carton Labeling |
|---|--|---|
| Name of manufacturer/distributor  | Manufactured for:<br>Celgene Corporation | Adequate                                  |
| Medication Guide (if applicable)  | NA                                       | NA  |
| No text on Ferrule and Cap over seal  | NA                                       | NA  |
| When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label. | NA                                       | NA  |
| And others, if space is available   | NA                                       | NA  |

**Assessment of Carton and Container Labeling: Adequate**

***Any deficiencies should be listed at the end in the “ITEMS FOR ADDITIONAL ASSESSMENT.”***

**ITEMS FOR ADDITIONAL ASSESSMENT**

**Adequate, pending the Applicant's acceptance of the revisions noted above in red.**

***Overall Assessment and Recommendation:***

**This application is recommended for approval per labeling/labels perspective once the following changes have been made to the label.**



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Chiou

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Wendy  
Wilson- Lee

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## CHAPTER VI: BIOPHARMACEUTICS

|   |   |
|---|---|
| <b>NDA Number</b>                               | 209899-Resub-13; 505 (b) (1) NME  |
| <b>Assessment Cycle Number</b>                  | 1   |
| <b>Drug Product Name/ Strength</b>              | ZEPOSIA® (ozanimod) capsules, 0.23 mg, 0.46 mg, and 0.92 mg                             |
| <b>Dosage Form</b>                              | Immediate Release Capsules  |
| <b>Route of Administration</b>                  | Oral Administration<br>(Dose escalate to recommended dose of 0.92 mg orally once daily) |
| <b>Applicant Name</b>                           | Celgene Corporation   |
| <b>Therapeutic Classification/ OND Division</b> | Immunosuppressive drug;<br>CDER/ON/DN2  |
| <b>Proposed Indication</b>                      | For the treatment of adult with relapsing forms of multiple sclerosis (MS)              |

### REVIEW SUMMARY

This Biopharmaceutics review focuses on **1)** the evaluation of the adequacy of the proposed dissolution method and acceptance criterion, and **2)** formulation/drug product bridging throughout product development.

**Dissolution Method and Acceptance Criterion:** The proposed dissolution method [500 ml of 0.01 N HCl using USP Apparatus 1 (basket) at 100 rpm] and acceptance criterion [NLT (b) (4) % (Q) in 15 minutes] for the proposed drug product batch release and stability testing are acceptable. The dissolution risk is deemed low, based on the totality of information and data provided (b) (4)

**Bridging Throughout Product Development:** The proposed commercial and clinical formulations are different (b) (4). In addition, there are changes in manufacturing process and manufacturing site between the commercial and clinical drug products. The Applicant demonstrated the similarity in the dissolution profiles using different pH media (0.01N HCl, USP pH 1.2 buffer, pH 4.5 acetate buffer, FeSSIF (pH 5.0), and FaSSIF (pH 6.5)) to establish the bridging between the clinical and commercial batches. The product bridging is deemed adequate.

### CONCLUSION and RECOMMENDATION

From the Biopharmaceutics perspective, NDA 209899-Resub-13 for ZEPOSIA® (ozanimod) capsules, 0.23 mg, 0.46 mg, and 0.92 mg is recommended for APPROVAL.

**BIOPHARMACEUTICS ASSESSMENT**

**LIST of SUBMISSIONS BEING REVIEWED**

| eCTD # (SND #) | Received date | Document      |
|----------------|---------------|---------------|
| 0012 (13)      | 03/25/2019    | Re-submission |

**DRUG SUBSTANCE**

| Ozanimod HCl          |  |                  |                  |     |      |      |     |                  |     |
|-----------------------|--|------------------|------------------|-----|------|------|-----|------------------|-----|
| BCS Class designation | The Applicant submitted a BCS Class 1 designation request under IND 109159 for Ozanimod Oral Capsules. The FDA BCS Committee denied the Class 1 designation due to the deficiencies in the <i>in vitro</i> cell permeability assay and the incomplete dissolution in pH 6.8 phosphate buffer. Refer to the Biopharmaceutics Review in DARRTS dated 06/06/2017 and Advice Letter dated June 2017 for details. |                  |                  |     |      |      |     |                  |     |
| BCS solubility        | High solubility. The highest solubility values were reported at pH 5.1. Solubility across the pH range from 1.2 to 7.5 at 37 °C is sufficient to provide sink conditions for the highest strength dose of 1 mg [0.02-3.5 mg/mL vs. 0.004 mg/mL (1 mg/250 mL)].   |                  |                  |     |      |      |     |                  |     |
|                       | pH   | 1.2 <sup>1</sup> | 2.0 <sup>2</sup> | 3.0 | 4.1  | 5.1  | 6.0 | 6.8 <sup>3</sup> | 7.5 |
|                       | Solubility (µg/mL)   | 58               | 669              | 171 | 2819 | 3506 | 164 | 101              | 20  |
|                       | <sup>1</sup> Simulated gastric fluid   |                  |                  |     |      |      |     |                  |     |
|                       | <sup>2</sup> 0.01M HCl   |                  |                  |     |      |      |     |                  |     |
|                       | <sup>3</sup> Simulated intestinal fluid  |                  |                  |     |      |      |     |                  |     |
| Particle size         | d (0.9): NMT (b) (4) µm  |                  |                  |     |      |      |     |                  |     |
| Polymorphism          | (b) (4)  |                  |                  |     |      |      |     |                  |     |

**DRUG PRODUCT**

The proposed Ozanimod HCl immediate release capsules 0.25 mg, 0.50 mg, and 1.0 mg are (b) (4) hard gelatin capsules containing the active ingredient, Ozanimod HCl, and inactive ingredients, microcrystalline cellulose, (b) (4) colloidal silicon dioxide (b) (4), croscarmellose sodium (b) (4), and magnesium stearate (b) (4). The drug product is manufactured by (b) (4) (b) (4).

**DISSOLUTION**

**Reviewer's Overall Assessment:** ADEQUATE

**Proposed Dissolution Method and Acceptance Criterion:**

| USP Apparatus | Speed (RPM) | Medium     | Volume/Temp | Acceptance Criterion                       |
|---------------|-------------|------------|-------------|--|
| I (Basket)    | 100         | 0.01 N HCl | 500 mL/37°C | NLT <sup>(b) (4)</sup> % (Q) at 15 minutes |

**Dissolution Method Development:**



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### **Validation for Dissolution Method:**

An HPLC assay method (with UV detection at 280 nm) was used to quantify the drug in the dissolution samples. The Applicant reported that the HPLC method was validated with regard to specificity, linearity, accuracy, instrument repeatability, intermediate precision, solution stability, and robustness with respect to HPLC parameters (mobile phase, detection wavelength and column temperature) and dissolution medium (0.01 ±0.001 N HCl). For the evaluation of the adequacy of the validation of the analytical HPLC method (including the HPLC method used for dissolution testing), refer to the Drug Product Review.

### **Dissolution Acceptance Criterion:**

The proposed drug product meets the requirements (e.g., high solubility, Tmax not critical, dissolution testing conditions, etc.) for highly soluble drugs, per 2018 FDA dissolution guidance. In addition, a tighter acceptance criterion of Q = (b) (4) % at 15 minutes is applied compared to the recommended 30 minutes, which is acceptable.

## BRIDGING THROUGHOUT PRODUCT DEVELOPMENT

### **Reviewer's Overall Assessment:** ADEQUATE

The proposed registration/commercial (Formulation 3) and clinical formulations (Formulation 1 and Formulation 2) are different with regard to (b) (4); refer to **Table 2** of 3.2.P.2.2 Pharmaceutical Development). In addition, there are changes in manufacturing process (b) (4) and site (b) (4) between the registration/commercial and clinical products (refer to **Table 11** in 3.2.P.2.2 Pharmaceutical Development).

**Table 2: Composition of the Development and Registration/Commercial Formulations**

| Formulation Component                       | Composition (mg) |      |      |               |      |      |      |                         |      |         |
|---|------------------|------|------|---------------|------|------|------|-------------------------|------|---------|
|   | Development      |      |      |               |      |      |      | Registration/Commercial |      |         |
|   | Formulation 1    |      |      | Formulation 2 |      |      |      | Formulation 3           |      |         |
|   | Strengths (mg)   |      |      |               |      |      |      |                         |      |         |
|   | 0.1              | 0.25 | 0.5  | 1.0           | 0.25 | 0.5  | 1.0  | 0.25                    | 0.5  | 1.0     |
| Ozanimod HCl                                | 0.10             | 0.25 | 0.50 | 1.00          | 0.25 | 0.50 | 1.00 | 0.25                    | 0.50 | 1.00    |
| Microcrystalline cellulose, (b) (4)         |                  |      |      |               |      |      |      |                         |      | (b) (4) |
|   |                  |      |      |               |      |      |      |                         |      | (b) (4) |
| Colloidal silicon dioxide                   |                  |      |      |               |      |      |      |                         |      | (b) (4) |
| Croscarmellose sodium                       |                  |      |      |               |      |      |      |                         |      | (b) (4) |
| Magnesium stearate                          |                  |      |      |               |      |      |      |                         |      | (b) (4) |
| Total Theoretical Capsule Components Weight |                  |      |      |               |      |      |      |                         |      | (b) (4) |
| <b>Capsule Shell</b>                        |                  |      |      |               |      |      |      |                         |      | (b) (4) |
|   |                  |      |      |               |      |      |      |                         |      | (b) (4) |

**Table 11: Historical Overview of Ozanimod HCl Capsule Formulations**

| Year Implemented        | Formulation   | Packaging                           | Manufacturer             |
|-------------------------|---|-------------------------------------|--------------------------|
| 2010 –<br>Formulation 1 | Phase 1:<br><ul style="list-style-type: none"> <li>0.1, 0.25, and 1.0 mg in (b) (4) capsule</li> </ul> Phase 2/3:<br><ul style="list-style-type: none"> <li>0.25, 0.5 and 1.0 mg in (b) (4) capsule</li> </ul>                                      | HDPE bottles<br>(b) (4)             | (b) (4)                  |
| 2012 –<br>Formulation 2 | Phase 1/2/3<br><ul style="list-style-type: none"> <li>0.25, 0.5 and 1.0 mg in (b) (4) capsule</li> </ul>  | HDPE bottles<br>(b) (4)             | (b) (4)                  |
| 2016 –<br>Formulation 3 | Registration/Commercial formulation:<br><ul style="list-style-type: none"> <li>0.25 mg in (b) (4) capsule imprinted with ink</li> <li>0.5 mg in (b) (4) capsule imprinted with ink</li> <li>1.0 mg in (b) (4) capsule imprinted with ink</li> </ul> | HDPE bottles<br>(b) (4)<br>blisters | Celgene<br>International |

The Applicant provided the dissolution results in dissolution media of 0.01N HCl, USP pH 1.2 buffer, pH 4.5 acetate buffer, FeSSIF (pH 5.0), and FaSSIF (pH 6.5) showing that the dissolution rates were not influenced by the changes between Formulation 2 (clinical) and Formulation 3 (registration/commercial) (refer to **Figures 2-5** in 3.2.P.2.2 Pharmaceutical Development;  $f_2$  calculation is not required as the dissolution reached  $> (b) (4)\%$  in 15 or 20 minute). Note that the Applicant also performed the comparative dissolution test using water, and the dissolution in water for both clinical and commercial formulations are incomplete ( $< (b) (4)\%$ ), with high variability observed even at 60 minutes (%RSD from 8.5% to 24.3%).

**Figure 2: Formulation 2 (Clinical) versus Formulation 3 (Commercial) Batch Comparison Plots When Using 0.01N HCl as a Dissolution Medium**



**Figure 3: Formulation 2 (Clinical) versus Formulation 3 (Commercial) Batch Comparison Plots When Using pH 1.2 USP Buffer as a Dissolution Medium**



**Figure 4: Formulation 2 (Clinical) versus Formulation 3 (Commercial) Batch Comparison Plots When Using pH 4.5USP Acetate Buffer as a Dissolution Medium**



**Figure 5: Formulation 2 (Clinical) versus Formulation 3 (Commercial) Batch Comparison Plots When Using FeSSIF as a Dissolution Medium**



**Figure 6: Formulation 2 (Clinical) versus Formulation 3 (Commercial) Batch Comparison Plots When Using FaSSIF as a Dissolution Medium**



From a Biopharmaceutics perspective, the comparative dissolution profile data in multi-pH media are deemed adequate to support the multiple changes (b) (4) (b) (4) between the clinical (Formulation 2) and commercial (Formulation 3) drug products, based on assessment of the risks of the proposed drug product (b) (4) (b) (4) (b) (4). This Reviewer defer to the Clinical Pharmacology Review and Clinical Review for the supportive PK, efficacy and safety data for Formulations 1 and 2.



Qi  
Zhang

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Ta-Chen  
Wu

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