

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**219209Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

## NDA Executive Summary

### 1. Application/Product Information

|                                        |                                                                                                            |                |                                                             |
|----------------------------------------|------------------------------------------------------------------------------------------------------------|----------------|-------------------------------------------------------------|
| <b>NDA Number</b>                      | 219209                                                                                                     |                |                                                             |
| <b>Applicant Name</b>                  | Vertex Pharmaceuticals                                                                                     |                |                                                             |
| <b>Drug Product Name</b>               | Journavx (suzetrigine tablets)                                                                             |                |                                                             |
| <b>Dosage Form</b>                     | Tablet                                                                                                     |                |                                                             |
| <b>Proposed Strength(s)</b>            | 50 mg                                                                                                      |                |                                                             |
| <b>NDA Classification</b>              | Type 1 - NME                                                                                               |                |                                                             |
| <b>Route of Administration</b>         | Oral                                                                                                       |                |                                                             |
| <b>Maximum Daily Dose</b>              | 150 mg                                                                                                     |                |                                                             |
| <b>Rx/OTC Dispensed</b>                | Rx                                                                                                         |                |                                                             |
| <b>Proposed Indication</b>             | Treatment of moderate to severe acute pain in adults                                                       |                |                                                             |
| <b>Drug Product Description</b>        | Tablets: 50 mg, blue, film coated, (b) (4) tablets debossed with "VX50" on one side and plain on the other |                |                                                             |
| <b>Co-packaged product information</b> | N/A                                                                                                        |                |                                                             |
| <b>Device information</b>              | Description, performance attributes or N/A                                                                 |                |                                                             |
| <b>Storage Temperature/ Conditions</b> | 68°F to 77°F (20°C to 25°C); excursions permitted to 59°F to 86°F (15°C to 30°C)                           |                |                                                             |
| <b>Review Team</b>                     | <b>Discipline</b>                                                                                          | <b>Primary</b> | <b>Secondary</b>                                            |
|                                        | <i>Drug Substance</i>                                                                                      | Sharon Kelly   | Katie Duncan                                                |
|                                        | <i>Drug Product/ Labeling</i>                                                                              | Eric Bow       | Mariappan Chelliah (drug product)<br>Julia Pinto (labeling) |
|                                        | <i>Manufacturing</i>                                                                                       | Yongming Lu    | Jingbo Xiao                                                 |

|                 |                         |                    |             |
|-----------------|-------------------------|--------------------|-------------|
|                 | <i>Biopharmaceutics</i> | Moshe Honick       | Ta-Chen Wu` |
|                 | <i>Microbiology</i>     | N/A                | N/A         |
|                 | <i>Other (specify)</i>  | N/A                | N/A         |
|                 | <i>RBPM</i>             | Teicher Agosto     |             |
|                 | <i>ATL</i>              | Mariappan Chelliah |             |
| <b>Consults</b> | N/A                     |                    |             |

**2. Final Overall Recommendation - Approval**

**3. Action Letter Information**

- a. **Expiration Dating:** 24 months stored at 68°F to 77°F (20°C to 25°C); excursions permitted to 59°F to 86°F (15°C to 30°C)
- b. **Additional Comments for Action:** None

**4. Basis for Recommendation:**

**a. Summary of Rationale for Recommendation:**

*The Office of Pharmaceutical Quality (OPQ) recommends APPROVAL for NDA 219209 JOURNAVX (suzetrigine) 50 mg tablets. The applicant has provided adequate information to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all facilities associated with this application. The proposed labeling and labels have adequate information to meet the regulatory requirements.*

**b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes**

**Recommendation by Subdiscipline:**

- Drug Substance - Adequate**
- Drug Product - Adequate**
- Quality Labeling - Adequate**
- Manufacturing - Adequate**
- Biopharmaceutics - Adequate**
- Microbiology - N/A**

**Environmental Assessment: Review & EI Statement - Adequate**  
**QPA for EA(s): No**

**5. Life-Cycle Considerations**

**Established Conditions per ICH Q12: No**

**Comments:**

**Comparability Protocols (PACMP): Yes**  
**Comments:**

**Additional Lifecycle Comments:** The Office Pharmaceutical Manufacturing Assessment (OPMA) has lifecycle consideration comments for future surveillance inspections.

***Application Technical Lead Name and Date: Mariappan V Chelliah, 12/13/2024***



Mariappan  
Chelliah

Digitally signed by Mariappan Chelliah

Date: 12/13/2024 03:40:17PM

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|                 |                                      |
|-----------------|--------------------------------------|
| Title:          | NDA IQA Template CHAPTER IV-LABELING |
| Document ID:    | OPQ-ALL-TEM-0045                     |
| Effective Date: | 18 Sep 2023 Revision: 00             |
| Total Pages:    | 22                                   |



Template Revision: 03

## CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the NDA IQA Guide \(OPQ-ALL-WI-0006\)](#)

|                                |                                |
|--------------------------------|--------------------------------|
| <b>NDA Number</b>              | 219209                         |
| <b>Assessment Cycle Number</b> | <u>1</u>                       |
| <b>Drug Product Name</b>       | JOURNAVX (suzetrigine) tablets |

**Assessment Recommendation:** Choose an item.

| Item                             | Assessment Conclusion | SDN # where labeling is adequate (“N/A” otherwise) |
|----------------------------------|-----------------------|----------------------------------------------------|
| Prescribing Information Labeling | Adequate              | 40                                                 |
| Patient Information              | Adequate              | 40                                                 |
| Instruction for Use (IFU)        | N/A                   | n/a                                                |
| Container Labels                 | Adequate              | 4                                                  |
| Carton Labeling                  | Adequate              | 4                                                  |

**Brief Description of Outstanding Issues:**

**Submissions being reviewed:**

| Document Reviewed (eCTD #, SDN #) | Date Received | Information Provided                                  |
|-----------------------------------|---------------|-------------------------------------------------------|
| 0040                              | 10/23/24      | Prescribing Information Labeling, Patient Information |
| 0004                              | 5/30/24       | Carton/Container Labels                               |
|                                   |               |                                                       |

### 1.0 PRESCRIBING INFORMATION<sup>1</sup>

**Assessment of Product Quality Related Aspects of the Prescribing Information:**

<sup>1</sup> [Labeling Review Tool \(LRT\) \(March 2022\)](#), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

## 1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

*JOURNAVX (suzetrigine) tablets, for oral use*

*Initial U.S. Approval: 202X*

-----DOSAGE FORMS AND STRENGTHS-----

*Tablets: 50 mg (3)*

| Item                                                                                                                                                                                                                                                  | Item in Proposed Labeling<br>(choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments<br>(If an item is Inadequate, provide more details on the issues, as appropriate) |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| <b>Product Title in Highlights<sup>2</sup> [21 CFR 201.57(a)(2)]</b>                                                                                                                                                                                  |                                                                          |                                                                                                       |
| Established name(s) <sup>3</sup>                                                                                                                                                                                                                      | Choose an item.                                                          | JOURNAVX (suzetrigine) tablets, for oral use                                                          |
| Route(s) of administration                                                                                                                                                                                                                            | Adequate                                                                 | for oral use                                                                                          |
| Controlled drug substance symbol (if applicable)                                                                                                                                                                                                      | N/A                                                                      |                                                                                                       |
| Initial U.S. Approval [§201.57(a)(3)]                                                                                                                                                                                                                 | Adequate                                                                 | "202X"                                                                                                |
| <b>Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]</b>                                                                                                                                                                              |                                                                          |                                                                                                       |
| Dosage form(s) <sup>4</sup> and strength(s) in metric system <sup>5</sup>                                                                                                                                                                             | Adequate                                                                 | Tablets: 50 mg                                                                                        |
| If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). <sup>6</sup> | N/A                                                                      |                                                                                                       |

<sup>2</sup> Draft guidance: [Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format \(January 2018\)](#)

<sup>3</sup> Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

<sup>4</sup> Draft guidance: [Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format \(January 2018\)](#); USP <1151>; USP Nomenclature Guideline

<sup>5</sup> Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

<sup>6</sup> Guidance: [Naming of Drug Products Containing Salt Drug Substances \(June 2015\)](#); MAPP 5021.1

| <b>Item</b>                                                                                                                                                                                                                                    | <b>Item in Proposed Labeling</b><br>(choose “Adequate”, “Inadequate”, or “N/A”) | <b>Assessor’s Comments</b><br>(If an item is Inadequate, provide more details on the issues, as appropriate) |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored.” <sup>7</sup>                                                                                                        | N/A                                                                             |                                                                                                              |
| For injectable drug products for parenteral 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. <sup>8</sup> | N/A                                                                             |                                                                                                              |

**Assessment:** *Adequate*

## 1.2 FULL PRESCRIBING INFORMATION

### 2.1 Section 2 (DOSAGE AND ADMINISTRATION)<sup>9</sup>

#### 2 DOSAGE AND ADMINISTRATION

(b) (4)

<sup>7</sup> Guidance: [Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation \(March 2013\)](#)

<sup>8</sup> Guidance: [Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use \(October 2018\)](#); USP <659>

<sup>9</sup> See § 201.57(c)(3); draft guidance: [Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format \(January 2023\)](#); Labeling Review Tool (March 2022, page 25)

(b) (4)



| Item                                                                                                                                                                                                                                                         | Item in Proposed Labeling<br>(choose “Adequate”, “Inadequate”, or “N/A”) | Assessor’s Comments<br>(If an item is Inadequate, provide more details on the issues, as appropriate) |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| <b>DOSAGE AND ADMINISTRATION section</b>                                                                                                                                                                                                                     |                                                                          |                                                                                                       |
| Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food <sup>10</sup> , storage conditions needed to maintain the stability of the reconstituted or diluted product). | N/A                                                                      |                                                                                                       |
| Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).                                                                                     | Adequate                                                                 | For oral use. Swallow tablets whole and do not chew or crush                                          |
| For parenteral products: include statement: <i>“Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.”</i> <sup>11</sup>                           | N/A                                                                      |                                                                                                       |
| If there is a USP monograph for the drug product and it contains a labeling requirement, ensure                                                                                                                                                              | N/A                                                                      |                                                                                                       |

<sup>10</sup> Draft Guidance: [Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments](#)

<sup>11</sup> §201.57(c)(3)(iv)

| <b>Item</b>                                                                                                                                                                                                        | <b>Item in Proposed Labeling</b><br>(choose “Adequate”, “Inadequate”, or “N/A”) | <b>Assessor’s Comments</b><br>(If an item is Inadequate, provide more details on the issues, as appropriate) |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| the labeling requirement is fulfilled. <sup>12</sup> Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).                                                              |                                                                                 |                                                                                                              |
| For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug                                                                                       | N/A                                                                             |                                                                                                              |
| For hazardous products, include the statement “ <i>DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.</i> ” <sup>x</sup> with x numerical citation to “OSHA Hazardous Drugs.” | N/A                                                                             |                                                                                                              |

**Assessment:** Adequate

**1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)<sup>13</sup>**

**3 DOSAGE FORMS AND STRENGTHS**

Tablets: 50 mg, blue, film-coated, (b) (4) tablets debossed with “VX50” on one side and plain on the other.

| <b>Item</b>                               | <b>Item in Proposed Labeling</b><br>(choose “Adequate”, “Inadequate”, or “N/A”) | <b>Assessor’s Comments</b><br>(If an item is Inadequate, provide more details on the issues, as appropriate) |
|-------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| <b>DOSAGE FORMS AND STRENGTHS section</b> |                                                                                 |                                                                                                              |
| Available dosage form(s)                  | Adequate                                                                        | Tablet                                                                                                       |

<sup>12</sup> USP General Notices 2.30 Legal Recognition

<sup>13</sup> See § 201.57(c)(4); [Labeling Review Tool \(March 2022, page 29\)](#)

| <b>Item</b>                                                                                                                                                                                                                                                                                       | <b>Item in Proposed Labeling</b><br>(choose “Adequate”, “Inadequate”, or “N/A”) | <b>Assessor’s Comments</b><br>(If an item is Inadequate, provide more details on the issues, as appropriate) |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| Strength(s) in metric system                                                                                                                                                                                                                                                                      | Adequate                                                                        | 50 mg                                                                                                        |
| If the active ingredient is a salt, apply the USP Salt Policy per FDA <a href="#">Guidance</a> . Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement. | N/A                                                                             |                                                                                                              |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.                                                                                                               | Adequate                                                                        | blue, film-coated, (b) (4) tablets debossed with “VX50” on one side and plain on the other.                  |
| Assess if the tablet is scored. If product meets <a href="#">guidelines</a> and criteria for a scored tablet, state “functionally scored.”                                                                                                                                                        | N/A                                                                             |                                                                                                              |
| For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).                                            | N/A                                                                             |                                                                                                              |

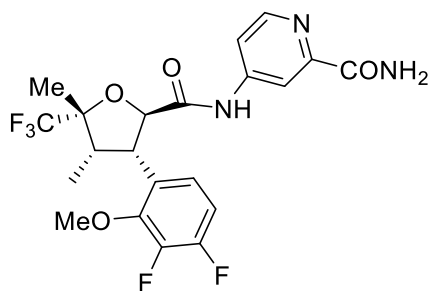
**Assessment:** *Adequate*

### 1.2.3 Section 11 (DESCRIPTION)<sup>14</sup>

<sup>14</sup> See § 201.57(c)(12); [Labeling Review Tool \(March 2022, page 56\)](#)

**11 DESCRIPTION**

The active ingredient in JOURNAVX tablets is suzetrigine, a sodium channel blocker, which has the following chemical name: 4-[(2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)oxolane-2-amido]pyridine-2-carboxamide. Its molecular formula is C<sub>21</sub>H<sub>20</sub>F<sub>5</sub>N<sub>3</sub>O<sub>4</sub> (b) (4) molecular weight is 473.39 g/mol. Suzetrigine has the following structural formula:



Suzetrigine is a white to off-white solid and is practically insoluble in water (b) (4)

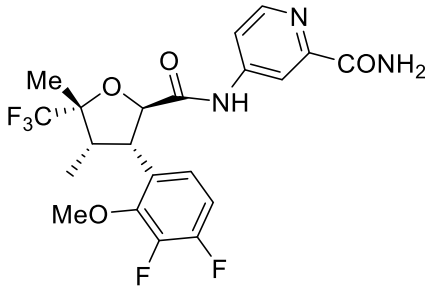
JOURNAVX is available as a blue, film-coated tablet for oral administration containing 50 mg of suzetrigine (b) (4) the following inactive ingredients: croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, and microcrystalline cellulose. The tablet film coat contains FD&C Blue #2 aluminum lake, polyethylene glycol, polyvinyl alcohol-partially hydrolyzed, talc, and titanium dioxide.

| Item                                                                       | Item in Proposed Labeling<br>(choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments<br>(If an item is Inadequate, provide more details on the issues, as appropriate) |
|----------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| <b>DESCRIPTION section</b>                                                 |                                                                          |                                                                                                       |
| Proprietary and established name(s) <sup>15</sup> [§ 201.57(c)(12)(i)(A)]. | Adequate                                                                 | The active ingredient in JOURNAVX tablets is suzetrigine                                              |
| Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].     | Adequate                                                                 | JOURNAVX is available as a blue, film-coated tablet for oral administration                           |

<sup>15</sup> Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

| <b>Item</b>                                                                                                                                                                                                                                                                                   | <b>Item in Proposed Labeling</b><br>(choose “Adequate”, “Inadequate”, or “N/A”) | <b>Assessor’s Comments</b><br>(If an item is Inadequate, provide more details on the issues, as appropriate)                                                                                                                                                                                              |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt <a href="#">Guidance</a> and <a href="#">MAPP</a> . For example: “TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)” [§ 201.57(c)(12)(i)(C)]. | N/A                                                                             |                                                                                                                                                                                                                                                                                                           |
| List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order. <sup>16</sup> Avoid brand names. [§ 201.57(c)(12)(i)(C)].                                                                                                               | Adequate                                                                        | (b) (4) the following inactive ingredients: croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, and microcrystalline cellulose. The tablet film coat contains FD&C Blue #2 aluminum lake, polyethylene glycol , polyvinyl alcohol-partially hydrolyzed, talc, and titanium dioxide |
| 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. [§ 201.100(b)(5)(iii)].                                                               | N/A                                                                             |                                                                                                                                                                                                                                                                                                           |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].                                                                                                                                               | N/A                                                                             |                                                                                                                                                                                                                                                                                                           |
| Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].                                                                                                                                                                                                                                  | N/A                                                                             |                                                                                                                                                                                                                                                                                                           |

<sup>16</sup> Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

| Item                                                                                                                                                   | Item in Proposed Labeling<br>(choose “Adequate”, “Inadequate”, or “N/A”) | Assessor’s Comments<br>(If an item is Inadequate, provide more details on the issues, as appropriate)                                                                                                                                                                                                                                                                                                               |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pharmacological/Therapeutic class <sup>17</sup> [§ 201.57(c)(12)(i)(E)].                                                                               | Adequate                                                                 | a sodium channel blocker                                                                                                                                                                                                                                                                                                                                                                                            |
| Chemical name <sup>18</sup> , structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].                                                            | Adequate                                                                 | <p>4-[(2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)oxolane-2-amido]pyridine-2-carboxamide</p> <p>Its molecular formula is C<sub>21</sub>H<sub>20</sub>F<sub>5</sub>N<sub>3</sub>O<sub>4</sub> (b) (4) molecular weight is 473.39 g/mol. Suzetrigine has the following structural formula:</p>  |
| If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].                                                                | N/A                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].                                                               | Adequate                                                                 | <p>Suzetrigine is a white to off-white solid and is practically insoluble in water</p> <p>(b) (4)</p>                                                                                                                                                                                                                                                                                                               |
| For oral prescription drug products, include gluten statement <sup>19</sup> (if applicable).                                                           | N/A                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”). | N/A                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                     |

<sup>17</sup> Listed before “indicated for” in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term “FDA EPC Text Phrases” in [FDA’s Labeling Resources for Human Prescription Drugs](#) for the most recent EPC list.

<sup>18</sup> Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

<sup>19</sup> Draft guidance: [Gluten in Drug Products and Associated Labeling Recommendations \(December 2017\)](#)

| Item                                                                                                                                                                                                                                   | Item in Proposed Labeling<br>(choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments<br>(If an item is Inadequate, provide more details on the issues, as appropriate) |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2). | N/A                                                                      |                                                                                                       |

**Assessment:** Adequate

**1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)<sup>20</sup>**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

JOURNAVX (suzetrigine) tablets are supplied as blue, filmcoated, (b) (4) tablets containing 50 mg of suzetrigine. Each tablet is debossed with the characters "VX50" on one side and plain on the other, and is packaged as follows:

- 30-count bottle NDC 51167-548-30
- 100-count bottle NDC 51167-548-31
- 100-count Hospital Unit Dose Carton (10 blister cards, each containing 10 tablets) NDC 51167-548-34

Store at 68°F to 77°F (20°C to 25°C); excursions permitted to 59°F to 86°F (15°C to 30°C) [see USP Controlled Room Temperature].

| Item                                             | Item in Proposed Labeling<br>(choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments<br>(If an item is Inadequate, provide more details on the issues, as appropriate) |
|--------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| <b>HOW SUPPLIED/STORAGE AND HANDLING section</b> |                                                                          |                                                                                                       |

<sup>20</sup> See § 201.57(c)(17); [Labeling Review Tool \(March 2022, page 70\)](#). Consider including proprietary name and established name.

| <b>Item</b>                                                                                                                                                                                                                                       | <b>Item in Proposed Labeling</b><br>(choose “Adequate”, “Inadequate”, or “N/A”) | <b>Assessor’s Comments</b><br>(If an item is Inadequate, provide more details on the issues, as appropriate)                                                                                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Available dosage form(s) [§ 201.57(c)(17)].                                                                                                                                                                                                       | Adequate                                                                        | JOURNAVX (suzetrigine) tablets are supplied as blue, filmcoated tablets containing 50 mg of suzetrigine                                                                                                                                          |
| Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA <a href="#">Guidance</a> . Clearly state whether the strength is based on the active moiety. No equivalency statement.   | Adequate                                                                        | containing 50 mg of suzetrigine                                                                                                                                                                                                                  |
| Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].                                                                                                                                                                             | Adequate                                                                        | <ul style="list-style-type: none"> <li>• 30-count bottle NDC 51167-548-30</li> <li>• 100-count bottle NDC 51167-548-31</li> <li>• 100-count Hospital Unit Dose Carton (10 blister cards, each containing 10 tablets) NDC 51167-548-34</li> </ul> |
| Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].                                                                 | Adequate                                                                        | JOURNAVX (suzetrigine) tablets are supplied as blue, filmcoated, (b) (4) tablets containing 50 mg of suzetrigine. Each tablet is debossed with the characters “VX50” on one side and plain on the other                                          |
| Assess if the tablet is scored. If product meets <a href="#">guidelines</a> and criteria for a scored tablet, state “functionally scored.”                                                                                                        | N/A                                                                             |                                                                                                                                                                                                                                                  |
| For injectable drug products for parenteral 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 (see USP <659>). | N/A                                                                             |                                                                                                                                                                                                                                                  |

| <b>Item</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                | <b>Item in Proposed Labeling</b><br>(choose "Adequate", "Inadequate", or "N/A") | <b>Assessor's Comments</b><br>(If an item is Inadequate, provide more details on the issues, as appropriate)                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| 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.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures. <sup>x</sup> " with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)] | N/A                                                                             |                                                                                                                                  |
| Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).                                                                                                                                                                                                                                                                                                                                  | Adequate                                                                        | Store at 68°F to 77°F (20°C to 25°C); excursions permitted to 59°F to 86°F (15°C to 30°C) [see USP Controlled Room Temperature]. |
| 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: " <i>Not made with natural rubber latex. Avoid statements such as "latex-free."</i> <sup>21</sup>                                                                                                                                                                 | N/A                                                                             |                                                                                                                                  |
| Include information about child-resistant packaging <sup>22</sup> (if chosen by manufacturer).                                                                                                                                                                                                                                                                                                                                                             | N/A                                                                             |                                                                                                                                  |

**Assessment:** *Adequate*

<sup>21</sup> Guidance: [Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex](#) (December 2014)

<sup>22</sup> Guidance: [Child-Resistant Packaging Statements in Drug Product Labeling](#) (August 2019)

### 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 review 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)<sup>23</sup>

| Item                                                                                                                       | Item in Proposed Labeling<br>(choose "Adequate" or "Inadequate") | Assessor's Comments<br>(If an item is Inadequate, provide more details on the issues, as appropriate) |
|----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| <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. | Choose an item.                                                  | (b) (4)                                                                                               |

**Assessment:** *Adequate*

## 2.0 PATIENT LABELING

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

| Item                                              | Item in Proposed Labeling<br>(choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments about Labeling<br>(If an item is Inadequate, provide more details on the issues, as appropriate) |
|---------------------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| Established name <sup>24</sup>                    | Adequate                                                                 | <b>JOURNAVX (jor na' vix)</b><br>(suzetrigine tablets), for oral use                                                 |
| Special preparation instructions (if applicable). | N/A                                                                      |                                                                                                                      |

<sup>23</sup> § 201.1(h)(5) and 201.1(i); [Labeling Review Tool \(March 2022, page 74\)](#)

<sup>24</sup> Established name = [Drug] [Route of Administration] [Dosage Form]

| <b>Item</b>                                                                                                                                                        | <b>Item in Proposed Labeling</b><br>(choose “Adequate”, “Inadequate”, or “N/A”) | <b>Assessor’s Comments about Labeling</b><br>(If an item is Inadequate, provide more details on the issues, as appropriate)                                                                                                                                                                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Storage and handling information (if applicable).                                                                                                                  | Adequate                                                                        | Store JOURNAVX at room temperature between 68°F to 77°F (20°C to 25°C).<br><b>Keep JOURNAVX and all medicines out of the reach of children.</b>                                                                                                                                                |
| If the product contains a desiccant, ensure the desiccant has a warning (e.g., “Do not eat.”) and the size and shape of the desiccant differ from the dosage form. | N/A                                                                             |                                                                                                                                                                                                                                                                                                |
| Active ingredient(s) (if applicable).                                                                                                                              | Adequate                                                                        | <b>Active ingredients:</b> suzetrigine.                                                                                                                                                                                                                                                        |
| Alphabetical listing of inactive ingredients (if applicable).                                                                                                      | Adequate                                                                        | <i>Inactive ingredients: croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, and microcrystalline cellulose. The tablet film coat contains FD&amp;C Blue #2 aluminum lake, polyethylene glycol, polyvinyl alcohol-partially hydrolyzed, talc, and titanium dioxide.</i> |
| Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.                                             | Adequate                                                                        | Manufactured for: Vertex Pharmaceuticals Incorporated; 50 Northern Avenue, Boston, MA 02210                                                                                                                                                                                                    |

**Assessment:** *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in “OUTSTANDING ISSUES AND RECOMMENDATIONS”**

**3.0 CONTAINER AND CARTON LABELING<sup>25</sup>**

<sup>25</sup> [Carton and Container Labeling Resources](#)

### 3.1 Container Labels<sup>26</sup>

*(Copy/paste or refer to a representative example of a proposed container label)*

#### **30-count bottles**



#### **100-count bottles**



#### **Blister backing:**

---

<sup>26</sup> Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

2 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

**100-count blister carton**

(b) (4)



| Item                                                             | Item in Proposed Carton Labeling<br>(choose "Adequate", "Inadequate", or "N/A") | Is item in Container Labels same as that of Carton Labeling? | Assessor's Comments about Container Labels and Carton Labeling<br>(If an item is Inadequate or different, provide more details, as appropriate) |
|------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Proprietary name and established name <sup>27</sup> , (font size | Adequate                                                                        | Yes                                                          | Journavx                                                                                                                                        |

<sup>27</sup> Established name = [Drug] [Route of Administration] [Dosage Form]

| Item                                                                                                                                                                           | Item in Proposed Carton Labeling<br>(choose "Adequate", "Inadequate", or "N/A") | Is item in Container Labels same as that of Carton Labeling? | Assessor's Comments about Container Labels and Carton Labeling<br>(If an item is Inadequate or different, provide more details, as appropriate) |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| and prominence) [§ 201.10(g)(2)].                                                                                                                                              |                                                                                 |                                                              |                                                                                                                                                 |
| Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)]. <sup>28</sup>                                                                                                     | Adequate                                                                        | Yes                                                          | 50 mg                                                                                                                                           |
| Route(s) of administration, not required for oral use [§ 201.100(b)(3)].                                                                                                       | Adequate                                                                        | Yes                                                          | For oral use only                                                                                                                               |
| If the active ingredient is a salt, include the equivalency statement per Salt <a href="#">Guidance</a> and <a href="#">MAPP</a> [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>]. | N/A                                                                             | Choose an item.                                              |                                                                                                                                                 |
| Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)]. <sup>29</sup>                                                                                               | Adequate                                                                        | Yes                                                          | 30 count, 100 count                                                                                                                             |
| "Rx only" displayed on the principal display [§ 201.100(b)(1)].                                                                                                                | Adequate                                                                        | Yes                                                          |                                                                                                                                                 |
| NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].                                                                                               | Adequate                                                                        | Yes                                                          |                                                                                                                                                 |
| Lot number and expiration date [§ 201.18 & 201.17].                                                                                                                            | Adequate                                                                        | Yes                                                          |                                                                                                                                                 |
| Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).                                                     | Adequate                                                                        | Yes                                                          | Store at 68°F to 77°F (20°C to 25°C); excursions permitted to 59°F to 86°F (15°C to 30°C) [see USP Controlled Room Temperature].                |
| For injectable drug products for parenteral administration, use appropriate package type                                                                                       | N/A                                                                             | Choose an item.                                              |                                                                                                                                                 |

<sup>28</sup> Express as "XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See [Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors \(May 2022\)](#)

<sup>29</sup> § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

| <b>Item</b>                                                                                                                                                                                                                 | <b>Item in Proposed Carton Labeling</b><br>(choose “Adequate”, “Inadequate”, or “N/A”) | <b>Is item in Container Labels same as that of Carton Labeling?</b> | <b>Assessor’s Comments about Container Labels and Carton Labeling</b><br>(If an item is Inadequate or different, provide more details, as appropriate) |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a “Not for direct infusion” statement. (See USP <659>). |                                                                                        |                                                                     |                                                                                                                                                        |
| Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].                                                                       | N/A                                                                                    | Choose an item.                                                     |                                                                                                                                                        |
| For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].          | N/A                                                                                    | Choose an item.                                                     |                                                                                                                                                        |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].                                                                             | N/A                                                                                    | Choose an item.                                                     |                                                                                                                                                        |
| Linear Bar code [§ 201.25(c)(2)]. <sup>30</sup>                                                                                                                                                                             | Adequate                                                                               | Yes                                                                 |                                                                                                                                                        |
| Adequate directions for use: “Recommended Dosage: See Prescribing Information” [§ 201.5 & 201.55].                                                                                                                          | Adequate                                                                               | Yes                                                                 |                                                                                                                                                        |
| Name of manufacturer/distributor                                                                                                                                                                                            | Adequate                                                                               | Yes                                                                 | Manufactured for:<br>Vertex Pharmaceuticals Incorporated                                                                                               |

<sup>30</sup> See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

| <b>Item</b>                                                                                                                                                                                                                                                                             | <b>Item in Proposed Carton Labeling</b><br>(choose “Adequate”, “Inadequate”, or “N/A”) | <b>Is item in Container Labels same as that of Carton Labeling?</b> | <b>Assessor’s Comments about Container Labels and Carton Labeling</b><br>(If an item is Inadequate or different, provide more details, as appropriate) |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| /packer [§ 201.1(a), 201.1(h)(5)].                                                                                                                                                                                                                                                      |                                                                                        |                                                                     | 50 Northern Ave, Boston, MA 02210                                                                                                                      |
| “Keep out of reach of children” statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].                                                                                                                                                                                       | Adequate                                                                               | Yes                                                                 | Keep out of reach and sight of children.                                                                                                               |
| If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.                                                                                                                                                                           | N/A                                                                                    | Choose an item.                                                     |                                                                                                                                                        |
| No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).                                                                                                                                                              | N/A                                                                                    | Choose an item.                                                     |                                                                                                                                                        |
| If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.                                                                                                                                                  | N/A                                                                                    | Choose an item.                                                     |                                                                                                                                                        |
| 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. <sup>31</sup> | N/A                                                                                    | Choose an item.                                                     |                                                                                                                                                        |
| And others if space is available.                                                                                                                                                                                                                                                       | N/A                                                                                    | Choose an item.                                                     |                                                                                                                                                        |

<sup>31</sup> USP General Notices 3.20 Indicating Conformance

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

***Any issues should be listed at the end in “OUTSTANDING ISSUES AND RECOMMENDATIONS”***

#### **4. OUTSTANDING ISSUES AND RECOMMENDATIONS**

*n/a*

*Primary Labeling Assessor Name and Date: Eric Bow Ph.D.*

*Secondary Assessor Name and Date (and Secondary Summary, as needed): Julia Pinto Ph.D.*



Eric  
Bow

Digitally signed by Eric Bow  
Date: 12/13/2024 01:36:33PM  
GUID: 5df160d800320e19970e198e30e1cc2e



Julia  
Pinto

Digitally signed by Julia Pinto  
Date: 12/13/2024 03:06:11PM  
GUID: 5050dbcb00001294a888a4bdc20a3a58

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|-----------------|-----------------------------------------------|-----------|----|
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**Important: Do Not Change the Header or Footer**

## CHAPTER VI: BIOPHARMACEUTICS

For more details about the items in this template, please see [Chapter VI \(Biopharmaceutics\) of the NDA IQA Guide](#)

|                                                 |                                                       |
|-------------------------------------------------|-------------------------------------------------------|
| <b>NDA Number</b>                               | 219209                                                |
| <b>Assessment Cycle Number</b>                  | 1                                                     |
| <b>Drug Product Name/ Strength</b>              | Journavx™ (suzetrigine) Tablets / 50 mg               |
| <b>Route of Administration</b>                  | Oral                                                  |
| <b>Applicant Name</b>                           | Vertex Pharmaceuticals Incorporated                   |
| <b>Therapeutic Classification/ OND Division</b> | Anesthesiology, Addiction Medicine, and Pain Medicine |
| <b>RLD/RS Number</b>                            | N/A                                                   |
| <b>Proposed Indication</b>                      | Moderate to severe acute pain in adults               |

### **Assessment Recommendation: Adequate**

#### **Assessment Summary:**

The Applicant seeks approval for the proposed Journavx™ (suzetrigine) Tablets, 50 mg under the 505(b)(1) pathway. The proposed indication is for the treatment of moderate to severe acute pain. The proposed drug product contains drug Suzetrigine (SUZ, VX-548, VRT-1737548), a first-in-class, (b) (4) non-opioid analgesic. The current applicant is supported by 18 clinical studies, with a pivotal Phase 3 program 2 placebo- and active-controlled Phase 3 studies in adults with moderate to severe pain. The proposed dose is two 50 mg tablets followed by one 50 mg tablet every 12 hours until pain resolves and can be taken without regard to food.

The proposed drug product containing drug substance, suzetrigine, that is practically insoluble in water (b) (4)

(b) (4)

(b) (4) The Biopharmaceutics review focuses on the evaluation and acceptability of 1) the proposed dissolution method and acceptance criterion, and 2) formulation bridging, with key findings summarized below:

**1. Dissolution test method and acceptance criterion:**

The dissolution test method was supported by a dissolution method development report submitted in seq 0003<sup>1</sup> with additional information provided in an Information Request (IR) response in seq 0025.<sup>2</sup> The Applicant proposed a dissolution test method using USP Apparatus 2 (paddle) at 65 RPM rotation speed in a 900 mL solution of 0.3 % Triton X-100 in 50 mM phosphate buffer, pH 6.8 (see Table 3). The dissolution parameters proposed by the Applicant were adequately justified by data provided in the development report and IR response. Additionally, the Applicant adequately demonstrated the discriminating ability or suitability of the proposed dissolution method towards varied (b) (4) content of the drug substance and varied material properties (b) (4). The proposed acceptance criterion is Q=(b) (4)% at 15 minutes, which is supported by dissolution profile data of the clinical/registration batches.

**2. Formulation Bridging:**

A total of four drug product batches were used in the Phase 3 trials. Three batches were the same in manufacture site, scale, and formulation as the final to-be-marketed (TBM) commercial product. One batch used initially in Phase 3 trials were produced at a smaller scale and at a different manufacturing site. Additionally, the (b) (4) (b) (4) was modified (b) (4) in the initial formulation to (b) (4) in the TBM formulation (b) (4). The Applicant provided full individual unit dissolution profiles (n=12) for all four batches used. All batches showed very rapid dissolution using the proposed dissolution method/test condition, with >85% dissolved at 15 minutes and without the need for f2 comparison. The initial formulation was therefore adequately bridged with the TBM formulation.

**Recommendation:**

From a Biopharmaceutics perspective, NDA-219209-ORIG-1 for Suzetrigine tablets 50 mg is adequate and recommended for **approval**.

FDA-approved dissolution method and acceptance criterion:

| Apparatus   | Speed  | Medium/Temperature                                          | Volume | Acceptance Criterion     |
|-------------|--------|-------------------------------------------------------------|--------|--------------------------|
| II (paddle) | 65 RPM | 0.3 % Triton X-100 in 50 mM phosphate buffer, pH 6.8/ 37 °C | 900 mL | Q=(b) (4)% at 15 minutes |

**List Submissions Being Assessed (table):**

| Document(s) Assessed | Date Received |
|----------------------|---------------|
| Seq 0001             | 3/28/2024     |
| Seq 0003             | 4/19/2024     |
| Seq 0025             | 9/5/2024      |
| Seq 0031             | 9/23/2024     |

**Highlight Key Issues from Last Cycle and Their Resolution: N/A**

**Concise Description of Outstanding Issues (list bullet points with key information and update as needed): N/A**

**B.1 BCS DESIGNATION**

**Assessment:**

The drug substance has low solubility (Table 1) and high permeability characteristics of BCS Class II drug, per BCS criteria (FDA’s M9 Guidance, ICH).

**Solubility:<sup>3</sup>**

Solubility data was studied across physiologic pH (pH 1-9), including water and simulated intestinal fluid (FaSSIR and FeSSIF), up to 48 hours, as presented in Table 1.

<sup>1</sup> \\CDSESUB1\EVSPROD\nda219209\0003\m3\32-body-data\32p-drug-prod\suzetrigine-tablet-50mg-all\32p2-pharm-dev\formulation-development.pdf

<sup>2</sup> \\CDSESUB1\EVSPROD\nda219209\0025\m1\us\quality-info-amend.pdf

<sup>3</sup> \\CDSESUB1\EVSPROD\nda219209\0025\m1\us\quality-info-amend.pdf

**Table 1: Solubility, Solution pH, and Physical Form of Suzetrigine Drug Substance in Aqueous Solutions and Organic Solvents at 24 and 48 hours**

| Solvent                              | Solubility after 24 hours (mg/ml) | Solubility after 48 hours (mg/ml) | pH after 24 hours | USP Definition <sup>a</sup> | Physical Form |
|--------------------------------------|-----------------------------------|-----------------------------------|-------------------|-----------------------------|---------------|
| pH 1.0 Buffer <sup>b</sup>           | 0.015                             | 0.016                             | 1.1               | practically insoluble       | (b) (4)       |
| pH 3.0 Buffer <sup>c</sup>           | ND                                | <0.002                            | 3.0               | practically insoluble       |               |
| pH 5.0 Buffer <sup>d</sup>           | ND                                | ND                                | 5.1               | practically insoluble       |               |
| pH 7.0 Buffer <sup>e</sup>           | ND                                | ND                                | 7.1               | practically insoluble       |               |
| pH 8.0 Buffer <sup>f</sup>           | ND                                | ND                                | 8.1               | practically insoluble       |               |
| pH 9.0 Buffer <sup>g</sup>           | 0.003                             | ND                                | 9.1               | practically insoluble       |               |
| Water at RT                          | ND                                | ND                                | 7.5               | practically insoluble       |               |
| Water at 37 °C                       | ND                                | ND                                | 7.9               | practically insoluble       |               |
| FaSSIF at 37 °C                      | <0.002                            | 0.002                             | 6.5               | practically insoluble       |               |
| FeSSIF at 37 °C                      | 0.023                             | 0.023                             | 5.9               | practically insoluble       |               |
| Methanol                             | 25.5                              | 25.0                              | --                | sparingly soluble           |               |
| Acetone                              | 178                               | 174                               | --                | freely soluble              |               |
| Tetrahydrofuran                      | 293                               | 291                               | --                | freely soluble              |               |
| Methanol/Tetrahydrofuran (70/30 v/v) | 118                               | 109                               | --                | freely soluble              |               |

Abbreviations: FaSSIF: Fasted State Simulated Intestinal Fluid; FeSSIF: Fed State Simulated Intestinal Fluid; RT: Room Temperature; ND: Not Detected (< 0.0006 mg/mL)  
<sup>a</sup> USP definitions: < 0.1 mg/mL: practically insoluble, 0.1-1 mg/mL: very slightly soluble, 1-10 mg/mL: slightly soluble, 10-30 mg/mL: sparingly soluble, 30-100 mg/mL: soluble, 100-1000 mg/mL: freely soluble.  
<sup>b</sup> Potassium chloride and hydrochloric acid  
<sup>c</sup> Potassium hydrogen phthalate and hydrochloric acid  
<sup>d</sup> Potassium hydrogen phthalate and sodium hydroxide  
<sup>e</sup> Potassium phosphate monobasic and sodium hydroxide  
<sup>f</sup> Sodium hydroxide and potassium phosphate monobasic  
<sup>g</sup> Potassium chloride, boric acid, and sodium hydroxide

**Permeability:**

Permeability was determined using the Caco- 2 cell model.<sup>4</sup> The apparent permeability in the A-B and B-A was 12.25 and 11.47x10<sup>-6</sup> cm/s, respectively (see Table 2). It was reported that the drug substance is highly permeable.

**Table 2: Baseline Permeability of VRT-1737548 across Caco-2 Cell Monolayer**

| Test Compounds       | Avg. P <sub>app</sub> (× 10 <sup>-6</sup> cm/sec) ± SD |              | Efflux Ratio | Avg. % Recovery ± SD |
|----------------------|--------------------------------------------------------|--------------|--------------|----------------------|
| *VRT-1737548<br>2 μM | AB                                                     | 12.25 ± 2.68 | 0.94         | 115.14 ± 7.84        |
|                      | BA                                                     | 11.47 ± 0.84 |              | 115.58 ± 2.95        |

\* Permeability assay was performed in the presence of 0.25% BSA.

**Dissolution:** See section B.2 [Dissolution Method and Acceptance Criterion]

## B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERION

### Assessment: Adequate

The Applicant provided an initial method development report (seq 0003)<sup>5</sup> with further data and clarification provided in an Information Request (IR) response (seq 0025)<sup>6</sup>. The method development process is summarized below and is deemed acceptable.

(b) (4)

<sup>4</sup> \\CDSESUB1\EVSPROD\nda219209\0001\m4\42-stud-rep\422-pk\4222-absorp\fdd-36383\fdd-36383.pdf

<sup>5</sup> \\CDSESUB1\EVSPROD\nda219209\0003\m3\32-body-data\32p-drug-prod\suzetrigine-tablet-50mg-all\32p2-pharm-dev\formulation-development.pdf

<sup>6</sup> \\CDSESUB1\EVSPROD\nda219209\0025\m1\us\quality-info-amend.pdf

<sup>7</sup><https://panorama.fda.gov/internal/document/preview?versionID=669eeb36000f61bbc9aa85c25d50ff30&ID=669eeb35000f6072a66bcb4a0a7a2c85>

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(b) (4)

***Discriminating Ability:***

In the initial submission (seq 0003), Applicant identified formulation variables that may impact dissolution (Table 4). Variations (b) (4)

(b) (4) identified as causing a medium risk of dissolution failure. (b) (4)

(b) (4)

(b) (4) The Applicant evaluated the ability of its proposed dissolution test method to discriminate based on these variables.

**Table 4: Dissolution Risk Assessment**

| Potential Failure Mode | Risk of Failure | Potential Cause | Formulation Variants for Discrimination Assessment |
|------------------------|-----------------|-----------------|----------------------------------------------------|
| (b) (4)                |                 |                 |                                                    |

Applicant varied tablet hardness from (b) (4) kp to evaluate its effect on dissolution. The target range is (b) (4) kp. All lots showed rapid to very rapid dissolution, with slower dissolution occurring at higher hardness levels (Figure 6). However, results of observed dissolution profiles were not sufficiently separated to demonstrate discriminating ability based on target range and changes made on the basis of tablet hardness.

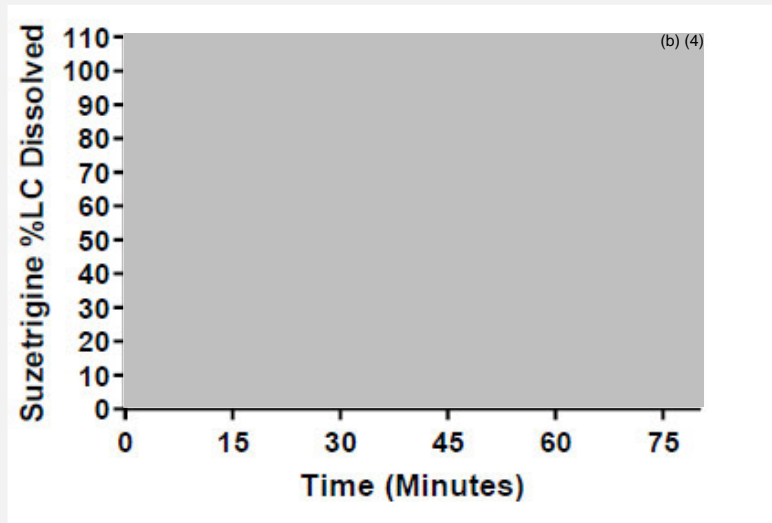


**Figure 6: USP Apparatus 2 Dissolution of 50 mg Suzetrigine Tablets Prepared with Different Tablet Hardnesses in 0.3% (v/v) Triton X-100 in 50 mM Sodium Phosphate, pH 6.8, 65 rpm**

Applicant also showed that the proposed dissolution test method does not discriminate based on level (b) (4) of the target level (b) (4) (b) (4) (Figure 7).

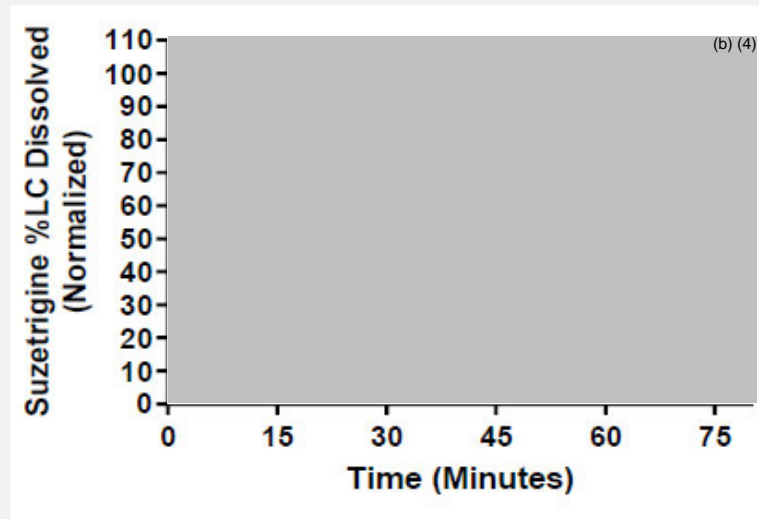


**Figure 7: USP Apparatus 2 Dissolution of 50 mg Suzetrigine Tablets Prepared with Different (b) (4) Levels in 0.3% (v/v) Triton X-100 in 50 mM Sodium Phosphate, pH 6.8, 65 rpm**

Applicant varied the level (b) (4) at a range of (b) (4) % of the target quantity. As reported, dissolution rate is inversely proportional to the (b) (4) level; however, dissolution profiles are considered similar to the target (Figure 8).

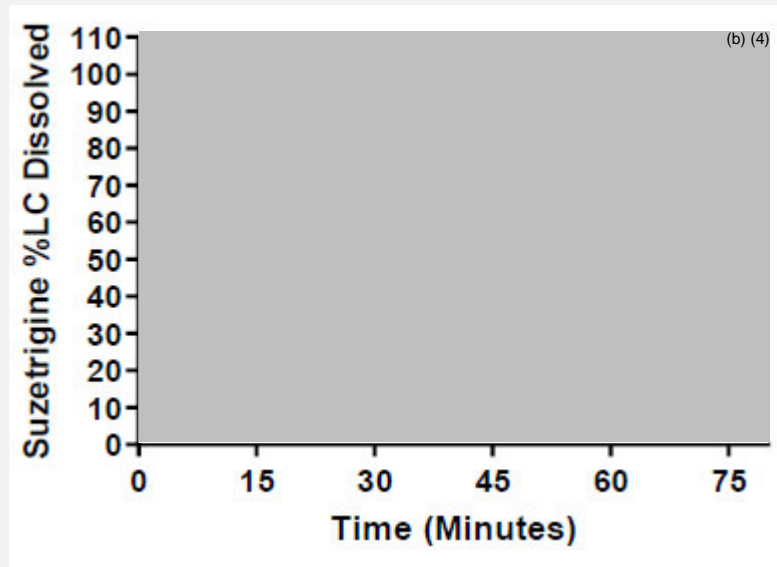


**Figure 8: USP Apparatus 2 Dissolution of 50 mg Suzetrigine Tablets Prepared with Different (b) (4) Levels in 0.3% (v/v) Triton X-100 in 50 mM Sodium Phosphate, pH 6.8, 65 rpm**

Additionally, the Applicant varied the (b) (4) properties (bulk density and particle size). The acceptance criterion for (b) (4) bulk density is (b) (4) g/mL<sup>8</sup> and DV50: (b) (4) μm for particle size.<sup>9</sup> Tablets produced with (b) (4) containing higher particle size and lower bulk density had slower dissolution (Figure 9).

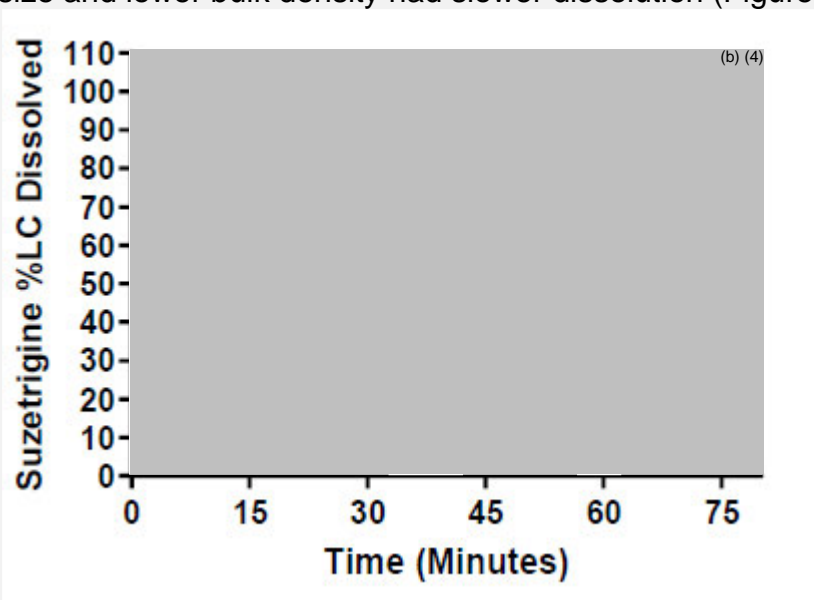


**Figure 9: USP Apparatus 2 Dissolution of 50 mg Suzetrigine Tablets Prepared with Different Suzetrigine (b) (4) Bulk Density and Particle Size in 0.3% (v/v) Triton X-100 in 50 mM Sodium Phosphate, pH 6.8, 65 rpm**

The Applicant also varied the level of (b) (4) suzetrigine in the 50 mg Suzetrigine Tablets at (b) (4)%. Tablets containing both (b) (4)% (b) (4) suzetrigine did not meet the proposed acceptance criterion, showing that the proposed dissolution test can discriminate based on (b) (4) content of the drug substance a level as low as (b) (4)% (Figure 10).

<sup>8</sup> \\CDSESUB1\EVSPROD\nda219209\0003\m3\32-body-data\32p-drug-prod\suzetrigine-sdd-250mg-g-all\32p5-contr-drug-prod\32p51-spec\specifications.pdf

<sup>9</sup> \\CDSESUB1\EVSPROD\nda219209\0003\m3\32-body-data\32p-drug-prod\suzetrigine-sdd-250mg-g-all\32p2-pharm-dev\pharmaceutical-development.pdf

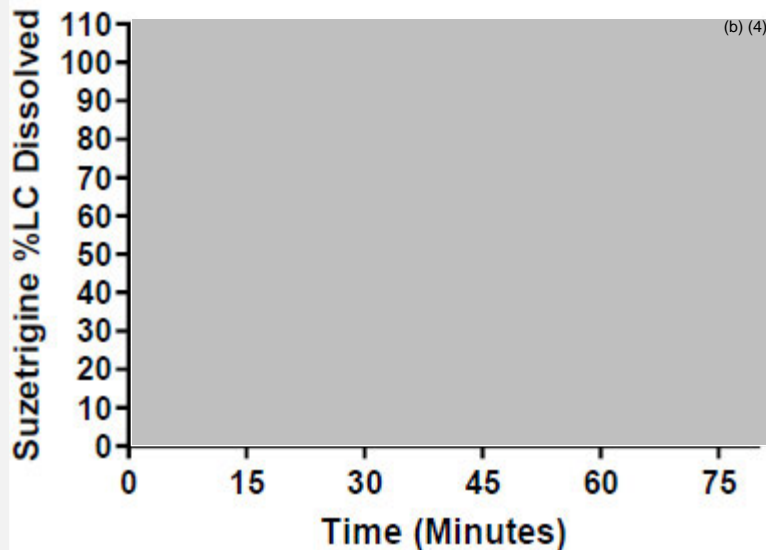


**Figure 10: USP Apparatus 2 Dissolution of 50 mg Suzetrigine Tablets Prepared with Different Levels of (b) (4) Suzetrigine in 0.3% (v/v) Triton X-100 in 50 mM Sodium Phosphate, pH 6.8, 65 rpm**

The IR sent on July 22, 2024 noted that some of the formulation variables (e.g., level of (b) (4)) that were varied to assess the discriminating ability of the dissolution test method were varied at a wider range than typically recommended (i.e., (b) (4) % of the target) that may not be meaningful. Applicant was requested to provide justification for the ranges tested. In response to the IR, the Applicant clarified that the formulation variables in question are not critical bioavailability attributes and are low risk for affecting dissolution performance based on their risk assessment. The finished product rapidly disintegrates, and therefore a very significant reduction in (b) (4) would be necessary for dissolution failure to occur. This Reviewer finds this to be an acceptable explanation.

The Applicant did demonstrate that the proposed dissolution test has discriminating ability for the formulation variables that were identified in the risk assessment as being medium risk for dissolution failure: (b) (4) (b) (4). Since the dissolution of the drug product and therefore its bioavailability depends primarily on the (b) (4) results are deemed reasonable.

In conclusion, the Applicant demonstrated acceptable discriminating ability of the proposed dissolution test (b) (4) (b) (4).

**Acceptance Criterion:**

The Applicant proposed an acceptance criterion of Q= (b) (4) % at 15 minutes. Based on the dissolution data provided on the four clinical batches (Tables 5-8), 15 minutes is the earliest timepoint at which all batches showed at least 85% dissolved. This is therefore an appropriate acceptance criterion.

**Table 5: USP Apparatus 2 Dissolution Results of 50 mg Suzetrigine Clinical Tablet Lot VMC.10568.00 in 0.3% (v/v) Triton X-100 in 50 mM Sodium Phosphate, pH 6.8, 65 rpm (n=12 compiled results)**

| Timepoint (Minutes) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Mean    | %RSD | Min | Max |  |
|---------------------|---|---|---|---|---|---|---|---|---|----|----|----|---------|------|-----|-----|--|
| 5                   |   |   |   |   |   |   |   |   |   |    |    |    | (b) (4) | 70   | 4.2 |     |  |
| 10                  |   |   |   |   |   |   |   |   |   |    |    |    | 91      | 2.6  |     |     |  |
| 15                  |   |   |   |   |   |   |   |   |   |    |    |    | 96      | 2.8  |     |     |  |
| 20                  |   |   |   |   |   |   |   |   |   |    |    |    | 98      | 3.0  |     |     |  |
| 30                  |   |   |   |   |   |   |   |   |   |    |    |    | 99      | 2.9  |     |     |  |
| 45                  |   |   |   |   |   |   |   |   |   |    |    |    | 99      | 2.8  |     |     |  |
| 60                  |   |   |   |   |   |   |   |   |   |    |    |    | 99      | 2.9  |     |     |  |
| 75                  |   |   |   |   |   |   |   |   |   |    |    |    | 100     | 2.8  |     |     |  |

**Table 6: Lot 5373325: Suzetrigine % LC Dissolved**

| Timepoint  | Replicate # |   |   |   |   |   |   |   |   |    |    |    | Mean    | %RSD | Min | Max |  |
|------------|-------------|---|---|---|---|---|---|---|---|----|----|----|---------|------|-----|-----|--|
|            | 1           | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |         |      |     |     |  |
| 5 minutes  |             |   |   |   |   |   |   |   |   |    |    |    | (b) (4) | 49   | 7.0 |     |  |
| 10 minutes |             |   |   |   |   |   |   |   |   |    |    |    | 75      | 3.3  |     |     |  |
| 15 minutes |             |   |   |   |   |   |   |   |   |    |    |    | 89      | 1.9  |     |     |  |
| 20 minutes |             |   |   |   |   |   |   |   |   |    |    |    | 95      | 1.2  |     |     |  |
| 30 minutes |             |   |   |   |   |   |   |   |   |    |    |    | 99      | 0.8  |     |     |  |
| 45 minutes |             |   |   |   |   |   |   |   |   |    |    |    | 101     | 0.7  |     |     |  |
| 60 minutes |             |   |   |   |   |   |   |   |   |    |    |    | 101     | 0.8  |     |     |  |

**Table 7: Lot 5373330: Suzetrigine % LC Dissolved**

| Timepoint  | Replicate # |   |   |   |   |   |   |   |   |    |    |    | Mean    | %RSD | Min | Max |  |
|------------|-------------|---|---|---|---|---|---|---|---|----|----|----|---------|------|-----|-----|--|
|            | 1           | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |         |      |     |     |  |
| 5 minutes  |             |   |   |   |   |   |   |   |   |    |    |    | (b) (4) | 54   | 4.0 |     |  |
| 10 minutes |             |   |   |   |   |   |   |   |   |    |    |    | 78      | 2.7  |     |     |  |
| 15 minutes |             |   |   |   |   |   |   |   |   |    |    |    | 90      | 1.5  |     |     |  |
| 20 minutes |             |   |   |   |   |   |   |   |   |    |    |    | 96      | 1.3  |     |     |  |
| 30 minutes |             |   |   |   |   |   |   |   |   |    |    |    | 100     | 1.3  |     |     |  |
| 45 minutes |             |   |   |   |   |   |   |   |   |    |    |    | 101     | 1.4  |     |     |  |
| 60 minutes |             |   |   |   |   |   |   |   |   |    |    |    | 101     | 1.3  |     |     |  |

**Table 8: Lot 5373333: Suzetrigine % LC Dissolved**

| Timepoint  | Replicate # |   |   |   |   |   |   |   |   |    |    |         | Mean | %RSD | Min | Max     |
|------------|-------------|---|---|---|---|---|---|---|---|----|----|---------|------|------|-----|---------|
|            | 1           | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12      |      |      |     |         |
| 5 minutes  |             |   |   |   |   |   |   |   |   |    |    | (b) (4) | 53   | 4.8  |     | (b) (4) |
| 10 minutes |             |   |   |   |   |   |   |   |   |    |    |         | 77   | 2.3  |     |         |
| 15 minutes |             |   |   |   |   |   |   |   |   |    |    |         | 89   | 1.5  |     |         |
| 20 minutes |             |   |   |   |   |   |   |   |   |    |    |         | 95   | 1.5  |     |         |
| 30 minutes |             |   |   |   |   |   |   |   |   |    |    |         | 99   | 1.6  |     |         |
| 45 minutes |             |   |   |   |   |   |   |   |   |    |    |         | 100  | 1.7  |     |         |
| 60 minutes |             |   |   |   |   |   |   |   |   |    |    |         | 100  | 1.6  |     |         |

**B.12 BRIDGING OF FORMULATIONS**

**Assessment: Adequate.**

Four batches of Suzetrigine 50 mg Tablet were used in the pivotal Phase 3 clinical trials as shown in Table 9. A minor change was made to the formulation during Phase 3 studies, (b) (4)

(b) (4) The overall composition was not changed. Tablet Lot VMC.10568.00 used the initial formulation (b) (4) (b) (4) with the remaining three tablet lots (5373325, 5373330, 5373333) representing the final to be marketed formulations. This represents a minor change that was supported with comparative dissolution data (Tables x-x). All four batches exhibited very rapid dissolution (i.e., >85% dissolved at 15 minutes) and can therefore be considered similar without f2 comparison.

**Table 9: Suzetrigine 50 mg tablets for clinical use- composition and manufacturing summary**

| Tablet Lot   | Manufacturer           | Batch Scale (Kg) | Manufacturing Process | Formulation                                 |
|--------------|------------------------|------------------|-----------------------|---------------------------------------------|
| VMC.10568.00 | Vertex Pharmaceuticals |                  | (b) (4)               | Initial Phase 3                             |
| 5373325      | (b) (4)                |                  |                       | Final Ph3 / Intended Commercial Formulation |
| 5373330      |                        |                  |                       |                                             |
| 5373333      |                        |                  |                       |                                             |

*Primary Biopharmaceutics Assessor’s Name and Date: Moshe Honick, Pharm.D., Ph.D., December 6, 2024*

*Secondary Assessor Name and Date (and Secondary Summary, as needed): Ta-Chen Wu, Ph.D., December 6, 2024*



Ta-Chen  
Wu

Digitally signed by Ta-Chen Wu  
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