CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214916Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 214916
Assessment # 1

Drug Product Name	KORSUVA (difelikefalin)
Dosage Form	Injection
Strength	65 mcg/1.3 mL (50 mcg/mL)
Route of Administration	Intravenous injection (IV bolus)
Rx/OTC Dispensed	Rx
Applicant	Cara Therapeutics, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA Submission	12/23/2020	All
Response to Clinical Information Request	01/27/2021	Clinical
Response to Clinical Information Request	03/12/2021	Clinpharm and Biometrics
Draft PI Labeling	03/19/2021	All
Quality Information - Stability	03/22/2021	ONDP
Clinical Safety Update	03/23/2021	Clinical
Response to Quality Information Request	04/01/2021	OPMA, DMA, and ONDP
Response to Clinical Information Request	04/06/2021	Clinpharm
Response to Clinical Information Request	04/23/2021	Clinpharm
Response to Clinical Information Request	04/30/2021	Clinical
Response to Quality Information Request	05/21/2021	OPMA
Container and Carton Labels	06/02/2021	All

Response to Quality Information Request	06/16/2021	ONDP
Container and Carton Labels	06/21/2021	All
Draft PI labeling	06/24/2021	All
Draft PI Labeling	07/14/2021	All
Container and Carton Labels	07/16/2021	All
Draft PI Labeling	07/30/2021	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Katharine Duncan, Ph.D.	Donna Christner, Ph.D.
Drug Product	Mark Seggel, Ph.D.	Wendy Wilson-Lee, Ph.D.
Manufacturing	Kumar Janoria, Ph.D.	Renee Marcsisin, Ph.D. Elizabeth Bearr, Ph.D.
Microbiology	Renee Marcsisin, Ph.D.	Elizabeth Bearr, Ph.D.
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Melinda Bauerlien, M.S.	
Application Technical Lead	Hamid Shafiei, Ph.D.	
Laboratory (OTR)	N/A	N/A
Environmental	Mark Seggel, Ph.D.	Wendy Wilson-Lee, Ph.D.

EXECUTIVE SUMMARY

For more details about the items in this template, please see the Executive Summary chapter of the NDA IQA Guide

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

- The applicant of this 505(b)(1) new drug application has provided **sufficient CMC information** to assure the identity, purity, strength, and quality of the drug substances, difelikefalin, and the drug product, KORSUVA (difelikefalin) Injection, 65mcg/1.3mL intended for intravenous (IV bolus) administration.
- Labels/labeling issues have been **satisfactorily** addressed.
- The Office of Pharmaceutical Manufacturing Assessment has made an overall "**Adequate**" recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion of the environmental assessment has been granted.

Therefore, from the OPQ perspective, this NDA is recommended for **APPROVAL** with the expiration dating period of **36 months**.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Cara Therapeutics, Inc. has submitted this 505 (b)(1) new drug application for KORSUVA (difelikefalin) Injection, 65mcg/1.3mL. This drug product is indicated for the treatment of moderate to severe pruritus in adult patients with chronic kidney disease undergoing hemodialysis.

The active ingredient, difelikefalin is small synthetic peptide and is a kappa opioid receptor agonist designed to act peripherally while have limited entry into the CNS. This active ingredient has not been previously approved or marketed in the United States and therefore, it has been classified as a new molecular entity. It is manufactured by (b) (4) (b) (4) It is a white to off-white amorphous powder and is freely soluble in water.

KORSUVA Injection is a sterile preservative-free clear colorless solution formulated in an isotonic 40mM acetate buffer for intravenous use. It is packaged in a single-dose vial containing 65 mcg of difelikefalin in 1.3 mL.

Each milliliter of KORSUVA injection contains 50 mcg/mL of difelikefalin equivalent to an average of 58.3 mcg/mL of difelikefalin acetate as the active ingredients and 1.3 mg of acetic acid, 2.5 mg of sodium acetate trihydrate, 7.2 mg of sodium chloride (to adjust tonicity), and water for injection as inactive ingredients.

KORSUVA injection is for intravenous bolus administration without dilution at the recommended dose of 0.5 mcg/kg into the venous line of the dialysis circuit at the end of each hemodialysis treatment. This drug product should be stored at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not freeze.

This drug product should be administered within 60 minutes after syringe preparation at room temperature of 20°C to 25°C (68°F to 77°F). The remaining unused portion of the drug product in the single-dose vial should be discarded.

Proposed Indication(s) including Intended Patient Population	Treatment of moderate to severe pruritus in adult patients with chronic kidney disease undergoing hemodialysis
Duration of Treatment	As prescribed by physician
Maximum Daily Dose	0.5mcg/kg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

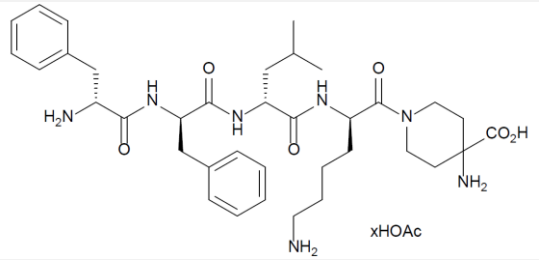
Drug Substance: Adequate

The drug substance, difelikefalin is a small synthetic peptide and kappa opioid receptor (KOR) agonist. This active ingredient has been developed and formulated as an injection drug product for intravenous bolus administration for treatment of moderate-to-severe pruritis associated with chronic kidney disease. Difelikefalin has not been previously approved as a drug or marketed in the United States and therefore, it has been classified as a new molecular entity (NME).

Difelikefalin is manufactured by [redacted] (b) (4) -

(b) (4)

Difelikefalin acetate is white to off-white lyophilized (b) (4) powder. It is highly hygroscopic and is freely soluble in water with pKa values of 2.4, 7.3, 8.9, and 10.2. Difelikefalin acetate has the chemical name, D-phenylalanyl-D-phenylalanyl-D-leucyl-D-lysyl-□-(4-N-piperidinyl)-amino-carboxylic acid, acetate salt, a molecular formula of $C_{36}H_{53}N_7O_6$ (as free base), a molecular mass of 679.(b) (4)g/mole (as free base), and the molecular structure below:



Difelikefalin acetate for this application is manufactured in accordance with the current Good Manufacturing Practices (cGMP) requirements by (b) (4). It is packaged in a (b) (4) and stored at (b) (4) C. It is tested, released, and accepted according to a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its proposed retest date of (b) (4) months. Sufficient stability data in support of the proposed retest date of (b) (4) months at the storage condition of (b) (4) ºC has been provided. The retest date of (b) (4) months is granted.

The drug substance module of this application has been reviewed by the Drug Substance Reviewer, Dr. Katharine Duncan. Dr. Duncan has found the drug substance information adequate and has recommended the approval of this application from the drug substance perspective. Dr. Duncan's review is provided in Drug Substance Chapter of the Integrated Quality Assessment (IQA).

Drug Product: Adequate

The drug product KORSUVA (difelikefalin) Injection for intravenous bolus administration is a sterile preservative-free clear colorless solution formulated in an isotonic 40mM acetate buffer. The active ingredient of this drug product, difelikefalin is a small synthetic peptide and kappa opioid receptor (KOR) agonist. KORSUVA is packaged in a single-dose

vial containing 65 mcg of difelikefalin in 1.3 mL. It is indicated for the treatment of moderate to severe pruritus in adult patients with chronic kidney disease undergoing hemodialysis. KORSUVA should be administered without dilution at the recommended dose of 0.5 mcg/kg into the venous line of the dialysis circuit at the end of each hemodialysis treatment.

Each milliliter of KORSUVA injection contains 50 mcg/mL of difelikefalin equivalent to an average of 58.3 mcg/mL of difelikefalin acetate as the active ingredients and 1.3 mg of acetic acid, 2.5 mg of sodium acetate trihydrate, 7.2 mg of sodium chloride (to adjust tonicity), and water for injection as inactive ingredients. Inactive ingredients used in the formulation of KORSUVA are all compendial materials.

KORSUVA injection is manufactured at (b) (4) and (b) (4) in accordance with current Good Manufacturing Practices (cGMP) and is tested against a specification that assures the identity, strength, purity, and quality of the drug product at release and throughout its proposed expiration dating period of 36 months. Sufficient stability data that supports the proposed expiration dating period of 36 months has been submitted to the application. Expiration dating period of 36 months is granted.

The drug product module of this application has been reviewed by the Drug Product Reviewer, Dr. Mark Seggel. Dr. Seggel has found the information provided in the drug product module of this application adequate and has recommended the approval of this application from drug product perspective. Dr. Seggel's review is provided in the Drug Product Chapter of the IQA.

The applicant's request for categorical exclusion from the preparation environmental assessment has also been reviewed by Dr. Mark Seggel. Dr. Seggel has found the applicant's request valid and has recommended granting the categorical exclusion to this application. The review of the categorical exclusion is also captured in the Drug Product Chapter of the IQA.

Labeling: Adequate

The CMC sections of the Prescribing Information (PI) as well as the immediate container and carton labels have been reviewed by the Drug Product Reviewer, Dr. Mark Seggel. Dr. Seggel has found the final PI as well as immediate container and carton labels submitted to this application satisfactory and recommended the approval of this application from the labeling/label perspective. Dr. Seggel's labeling/label review is provided in the Labeling Chapter of the IQA.

Manufacturing: Adequate

KORSUVA (difelikefalin) Injection is a sterile preservative-free clear colorless solution formulated in an isotonic 40mM acetate buffer.

The manufacturing process for this drug product starts with the [redacted] (b) (4)

The manufacturing process for this drug product has been reviewed by the Office of Pharmaceutical Manufacturing Assessment (OPMA) Reviewers, Dr. Kumar Janoria and Dr. Renee Marcsisin. Dr, Janoria and Dr. Marcsisin have found the manufacturing process for KORSUVA at both manufacturing sites, [redacted] (b) (4) adequate.

Dr. Janoria and Dr. Marcsisin have also reviewed the facilities involved in in this application and found all facilities adequate. Therefore, Dr. Janoria and Dr. Marcsisin have recommended the approval of this application from the OPMA perspective. Dr. Janoria's/Dr. Marcsisin's review is provided in the Manufacturing Chapter of the IQA.

Biopharmaceutics: Adequate

Not applicable. This is a solution for intravenous administration.

Microbiology (if applicable): Adequate

The proposed drug product in this application is a sterile solution for intravenous bolus administration without any dilution.

This drug product is produced at two commercial manufacturing sites, [redacted] (b) (4)

1) [redacted] (b) (4)

2) (b) (4)

The drug product sterilization process provided in the application as well as the related information provided in the referenced Type V DMF (b) (4), DMF (b) (4), and DMF (b) (4) have been reviewed by the Microbiology Reviewer, Dr. Renee Marcsisin. Dr. Marcsisin has found the information regarding the sterilization process adequate to support the approval of this application. Dr. Marcsisin's review is provided in the Microbiology Chapter of the IQA.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Drug Product (b) (4)	Adequacy of (b) (4)	H	(b) (4)	Very Low Acceptable	None

D. **List of Deficiencies:**

None

Application Technical Lead:

Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ

Hamid Shafiei

Digitally signed by Hamid Shafiei
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QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the NDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	Adequate	03/23/2007	No changes to the (b) (4) have been made since. Additional supporting information has been submitted in the NDA.
	V			Adequate	05/21/2021	Reviewed by Renee Marcsisin, Ph.D.
	V			Adequate	05/21/2021	Reviewed by Renee Marcsisin, Ph.D.
	V			Adequate	06/16/2020	Dustin Thomas, Ph.D.

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

Document	Application Number	Description
IND	123140	CMC Information
		(b) (4)

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER IV: LABELING

Labeling Submissions Assessed	Document Date
Original Submission (SN 0001)	12/23/2020
Labeling/Package Insert Draft (Word version) (SN 0004)	03/19/2021
Labeling/Container-Carton Draft (SN 0012)	06/02/21
Labeling/Container-Carton Draft (SN 0014)	06/18/2021
Labeling/Package Insert Draft (SN 0015)	06/24/2021
Labeling/Package Insert Draft (SN 0016)	07/14/2021
Labeling/Container-Carton Draft (SN 0017)	07/16/2021

Associated Labeling Reviews	Document Date
DMEPA Review	07/08/2021
OPDP / DDMAC Review	05/28/2021
DMEPA Review	04/06/2021
DMEPA Proprietary Name Review	03/18/2021

1.0 PRESCRIBING INFORMATION

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

From the product quality perspective, the initially proposed prescribing information (PI) was deficient in several areas.

Throughout the proposed labels and labeling the Applicant (Cara) refers to the product as a (b) (4) However, per the October 2018 Guidance for Industry, *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*, the appropriate package type is single-dose container (vial). Cara has revised the labels and labeling accordingly.

The drug product is dosed on a microgram per kilogram (0.5 mcg/kg) basis. A table listing body weight ranges and injection volume is provided in Section 2. A patient weighing 36 kg would require a 0.4 mL injection while a patient weighing 204 kg would require a 2 mL injection. The vials (b) (4) (b) (4) the product strength is 65 mcg / 1.3 mL (50 mcg / mL). Note: DMEPA raised

concerns about potential confusion resulting from the expression of strength on a [redacted] (b) (4) DMEPA therefore recommended that difelikefalin weight be expressed as micrograms (mcg) throughout the labeling. The labels and labeling have been revised accordingly.

Although the active ingredient was identified as the acetate salt of difelikefalin, no equivalency statement was provided. Because the acetate content varies across drug substance batches (x HOAc, where 1≤ x ≤2), the Applicant initially rejected the idea of including an equivalency statement. The Applicant was advised that a salt equivalency statement was required, and recommended language, including options for using a range (calculated where x = 1 to x =2) or stating an average, was provided. Satisfactory language was adopted and included in Section 11 Description (and on the carton label; space limitations preclude inclusion on the vial label).

Revisions were made to the list of inactive ingredients in Section 11 (and on the carton) to meet requirements for parenteral products.

The propose storage statement was incomplete as proposed. It has been adequately revised and now includes degrees Fahrenheit.

The labeling submitted under SN 0016 adequately incorporates the OPQ and OND review team's recommendations for revisions to the product quality related aspects of the prescribing information. Overall, the revised prescribing information, as submitted under SN 0016, satisfies the product quality related labeling requirements in 21 CFR 201.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proposed (SN 0001): **KORSUVA® (difelikefalin) injection, for intravenous use**		
Product Title	Adequate	Presentation consistent with Product Title guidance.
Proprietary name	Adequate	KORSUVA acceptable per DMEPA 03/18/2021
Established name(s)	Adequate	DS: difelikefalin (USAN 2016) DP: difelikefalin injection
Route(s) of administration	Adequate	intravenous
SN 0016: As proposed in SN 0001		

Dosage and Administration in Highlights		
Proposed (SN 0001): • Do not mix or dilute KORSUVA prior to administration. (2.2) [redacted] (b) (4)		
Dosage	Inadequate	No information about weight-based dosing provided (microgram per kg). DMEPA recommends that strength, etc., be expressed on mcg-basis throughout the labeling for consistency.
Special Instructions	Inadequate	Should include comment about use of product within 60 minutes of syringe preparation.
SN 0016: • Recommended dosage is 0.5 mcg/kg. (2.1) • Administer by intravenous bolus injection into the venous line of the dialysis circuit at the end of each HD treatment. (2.1) • Do not mix or dilute KORSUVA prior to administration. (2.2) • Administer within 60 minutes of syringe preparation. (2.3) • See full prescribing information for additional recommendations on preparation and administration of KORSUVA. (2.2, 2.3)		
Dosage Forms and Strengths Heading in Highlights		
Proposed (SN 0001): Injection: [redacted] (b) (4) mL solution in a [redacted] (b) (4) glass vial. (3)		
Summary of the dosage form(s) and strength(s) in metric system.	Inadequate	As noted above, DMEPA recommends use of mcg throughout the labeling. Strength should be expressed as: 65 mcg/1.3 mL (50 mcg/mL). [redacted] (b) (4)

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Inadequate	Inadequate. Although the dose is based on patient weight, the product is a "**single-dose**" vial. The unused portion should be discarded.
Revised (SN 0016): ----------**DOSAGE AND ADMINISTRATION**---------- • Recommended dosage is 0.5 mcg/kg. (2.1) • Administer by intravenous bolus injection into the venous line of the dialysis circuit at the end of each HD treatment. (2.1) • Do not mix or dilute KORSUVA prior to administration. (2.2) • Administer within 60 minutes of syringe preparation. (2.3) • See full prescribing information for additional recommendations on preparation and administration of KORSUVA. (2.2, 2.3) ----------**DOSAGE FORMS AND STRENGTHS**---------- *Injection*: 65 mcg /1.3 mL(50 mcg/mL) of difelikefalin (3)		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Proposed (SN 0001): 2.2 Preparation Instructions • Do not mix or dilute KORSUVA prior to administration. (b) (4) Inspect KORSUVA for particulate matter and discoloration prior to administration. Do not use KORSUVA vials if particulate matter or discoloration is observed. • (b) (4) Discard any unused product. • Injection volume to be administered is determined by patient's target dry body weight in kilograms. See Table 1 (b) (4) 2.3 Administration Instructions … • The dose must be administered within 60 minutes of the completion of the syringe preparation.		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Inadequate	Product is a "**single-dose**" vial.

Revised (SN 0016):

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

- The recommended dosage of KORSUVA is 0.5 mcg/kg administered by intravenous bolus injection into the venous line of the dialysis circuit at the end of each HD treatment *[see Dosage and Administration (2.3)]*.
- If a regularly scheduled HD treatment is missed, resume KORSUVA at the end of the next HD treatment.

2.2 Preparation Instructions

- Do not mix or dilute KORSUVA prior to administration.
- Inspect KORSUVA for particulate matter and discoloration prior to administration. The solution should be clear and colorless. Do not use KORSUVA vials if particulate matter or discoloration is observed.
- KORSUVA is supplied in a single-dose vial. Discard any unused product.
- Injection volume to be administered is determined by patient's target dry body weight in kilograms (one patient may use less than the full contents of the vial or use more than one vial). See Table 1.

Table 1. KORSUVA Injection Volumes Based on Target Dry Body Weight

Target Dry Body Weight Range (kg)	Injection Volume (mL)*
36 – 44	0.4
45 – 54	0.5
55 – 64	0.6
65 – 74	0.7
75 – 84	0.8
85 – 94	0.9
95 – 104	1
105 – 114	1.1
115 – 124	1.2
125 – 134	1.3
135 – 144	1.4
145 – 154	1.5
155 – 164	1.6
165 – 174	1.7
175 – 184	1.8
185 – 194	1.9
195 – 204	2

* Total Injection Volume (mL) = Patient Target Dry Body Weight (kg) x 0.01, rounded to the nearest tenth (0.1 mL). For patient target dry body weight outside of the ranges in Table 1, use this formula.

2.3 Administration Instructions

- KORSUVA is removed by the dialyzer membrane and must be administered after blood is no longer circulating through the dialyzer.
- Administer KORSUVA by intravenous bolus injection into the venous line of the dialysis circuit at the end of each HD session.
    - The dose may be given either during or after rinse back of the dialysis circuit.
    - If the dose is given after rinse back, administer KORSUVA into the venous line followed by at least 10 mL of normal saline flush.
    - If the dose is given during rinse back, no additional normal saline is needed to flush the line.
- The dose must be administered within 60 minutes of the completion of the syringe preparation. Discard any unused product.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Proposed (SN 0001): (b) (4)		
Available dosage form(s)	Adequate	At this time only one dosage form is proposed.
Strength(s) in metric system	Inadequate	As already noted, the strength should be expressed as: 65 mcg/1.3 mL (50 mcg/mL)
(b) (4)		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Inadequate	Package type is "**single-dose"** vial.

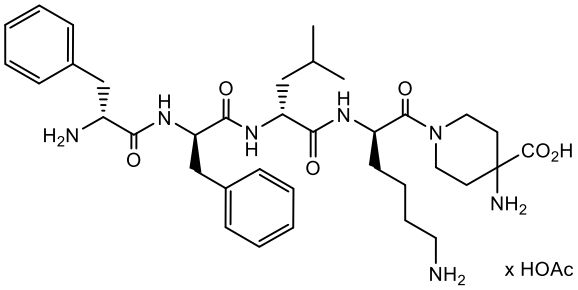
Revised (SN 0016):

3 DOSAGE FORMS AND STRENGTHS

Injection: 65 mcg/1.3 mL (50 mcg/mL) of difelikefalin as a clear, colorless solution in a single-dose glass vial.

1.2.3 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proposed (SN 0001): **11 DESCRIPTION** KORSUVA (difelikefalin) is a [redacted](b)(4) kappa opioid receptor agonist. [redacted](b)(4) is a white to off-white powder with a molecular formula of $C_{36}H_{53}N_7O_6$•xAcOH ($1.0 \leq x \leq 2.0$) and a molecular weight of 679.4 g/mol (mono-isotopic; free base). [redacted](b)(4) is a single stereoisomer present as an acetate salt. It is soluble in water. [redacted](b)(4) The chemical structure is:  KORSUVA (difelikefalin) injection is supplied in a [redacted](b)(4) vial containing [redacted](b)(4) of [redacted](b)(4) as a sterile, preservative-free, [redacted](b)(4) clear and colorless solution for intravenous injection. [redacted](b)(4) KORSUVA is formulated as an isotonic 40 mM acetate buffer solution with an osmolality of 250 to 350 mOSM and a pH of 4.5. Each milliliter of KORSUVA injection contains [redacted](b)(4) 7.2 mg of sodium chloride, 1.3 mg of acetic acid and 2.5 mg of sodium acetate trihydrate.		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Inadequate	Salt equivalency statement needs to be added. Cara did not include because it will vary from batch to batch.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Adequate	

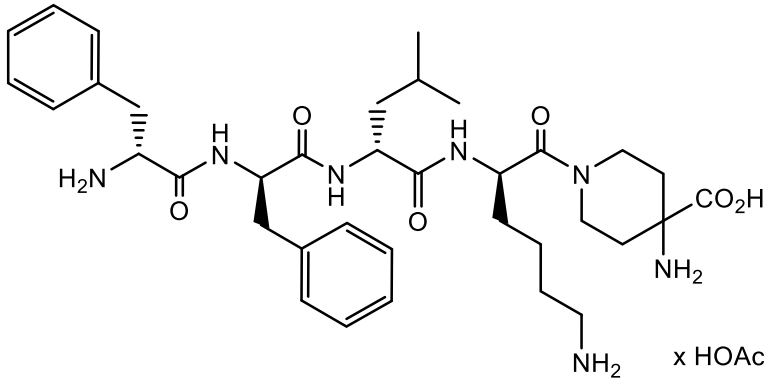
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Inadequate	List in alphabetical order, add function of NaCl as tonicity agent.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	Adequate	
Pharmacological/ therapeutic class	Inadequate	OND recommends simply "kappa opioid receptor agonist"
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	• pH 4.5 • osmolality 250-350 mOSM
For oral prescription drug products, include gluten statement 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	

Revised (SN 0016):

11 DESCRIPTION

KORSUVA (difelikefalin) is a kappa opioid receptor agonist. Difelikefalin is a synthetic peptide with a single stereoisomer and is present as an acetate salt. Difelikefalin acetate is a white to off-white powder with a molecular formula of $C_{36}H_{53}N_7O_6$•xAcOH ($1.0 \leq x \leq 2.0$) and a molecular weight of 679.4 g/mol (mono-isotopic; free base). It is soluble in water. The chemical name of difelikefalin acetate is 4-amino-1-(D-phenylalanyl-D-phenylalanyl-D-leucyl-D-lysyl)piperidine-4-carboxylic acid, acetate salt.

The chemical structure is:



KORSUVA (difelikefalin) injection is supplied in a single-dose vial containing 65 mcg/1.3 mL (50 mcg/mL) of difelikefalin as a sterile, preservative-free, clear and colorless solution for intravenous injection.

KORSUVA is formulated as an isotonic 40 mM acetate buffer solution with an osmolality of 250 to 350 mOSM and a pH of 4.5.

Each milliliter of KORSUVA injection contains 50 mcg of difelikefalin (equivalent to an average of 58.3 mcg of difelikefalin acetate), 1.3 mg of acetic acid, 2.5 mg of sodium acetate trihydrate, 7.2 mg of sodium chloride (to adjust tonicity), and water for injection.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Proposed (SN 0001): **16 HOW SUPPLIED/STORAGE AND HANDLING** (b) (4) NDC XXXXX-XX-XX: (b) (4) . <u>Storage</u> (b) (4) with excursions to 15º to 30ºC (see USP Controlled Room Temperature). (b) (4) within 60 minutes of syringe preparation; prepared syringes can be stored at ambient temperature until dosing. (b) (4) Any unused drug remaining after injection must be discarded.		
Product name	Inadequate	Only proprietary name presented. Add established name.
Available dosage form(s)	Inadequate	Dosage form: Injection (b) (4) (b) (4)
Strength(s) in metric system	Inadequate	Revise to: 65 mcg/1.3 mL (50 mcg/mL)
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Inadequate	"**single-dose**" vials; revise to (b) (4) (1.3 mL), (b) (4) NDC TBD

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Inadequate	Package type: “**single-dose**”
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.)	Adequate	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Inadequate	Revise to Store vials at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not freeze.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid	N/A	

statements such as “latex-free.”		
Include information about child-resistant packaging	N/A	

Revised (SN 0016):

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied
KORSUVA (difelikefalin) injection is supplied as a sterile, clear and colorless solution in 1.3 mL single-dose, glass vials:

NDC 59353-065-01: 65 mcg/1.3 mL (50 mcg/mL) single-dose vial

NDC 59353-065-12: Carton containing 12 vials

Storage and Handling
Store vials at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not freeze.

KORSUVA injection must be administered within 60 minutes of syringe preparation; prepared syringes can be stored at ambient temperature 20°C to 25°C (68°F to 77°F) until dosing *[see Dosage and Administration (2.2, 2.3)]* .

1.2.5 Other Sections of Labeling

N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Proposed (SN 0001): Manufactured for: Cara Therapeutics, Inc. Stamford, CT 06902 Marketed by: (b) (4)		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Adequate	
SN 0016: Manufactured for: Cara Therapeutics, Inc. Stamford, CT 06902 Marketed by: Vifor (International) Inc., Rechenstrasse 37, 9014 St. Gallen, Switzerland		

2.0 PATIENT LABELING

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

Not Applicable – This product is not dispensed to patients for self-administration.

3.0 CARTON AND CONTAINER LABELING

Assessment of Carton and Container Labeling: *ADEQUATE*

The same deficiencies identified in the originally proposed prescribing information occur in the proposed (SN 0001) vial and carton labels. Those deficiencies, along with other recommendations from DMEPA and OPDP, were communicated to Cara. The recommended revisions have been adequately incorporated into the vial and carton labels as submitted under SN 0017.

3.1 Container Label

Item	Items in Proposed Labeling	Assessor's Comments
		(b) (4)

Proprietary name, established name, and dosage form (font size and prominence	Adequate	
Dosage strength	Inadequate	Revise to: 65 mcg/1.3 mL (50 mcg/mL)
Route of administration	Inadequate	Intravenous
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Adequate	not included due to space limitation
Net contents (e.g., tablet count, volume of liquid)	Inadequate	1.3 mL [redacted] (b) (4)
“Rx only” displayed	Adequate	
NDC number	Inadequate	Space allotted for NDC; actual NDC TBD
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the labeling for the user to write the new BUD.	Inadequate	Store at 20°C to 25°C (68°F to 77°F)
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Inadequate	Package type is: “single-dose”
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar Code	Inadequate	Linear bard code required
Name of manufacturer / distributor	Adequate	
No text on Ferrule and Cap overseal	Adequate	

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.	N/A	
And others, if space is available	N/A	
Revised (SN 0017):		

(b) (4)

[redacted]

3.2 Carton Labeling

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling	Assessor's Comments about Carton Labeling

APPEARS THIS WAY ON ORIGINAL

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Proprietary name, established name, and dosage form (font size and prominence)	Adequate	
Dosage strength	Inadequate	Revise to: 65 mcg/1.3 mL (50 mcg/mL)
Route of administration	Inadequate	Intravenous
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Inadequate	Salt equivalency statement consistent with PI should be added.
Net contents (e.g., tablet count, volume of liquid)	Inadequate	1.3 mL (b) (4)
"Rx only" displayed on the principal display	"RX ONLY"	
NDC number	Inadequate	NDC TBD
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Inadequate	Revise to Store vials at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not freeze.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Inadequate	Package type: single-dose
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar Code	Adequate	

Name of manufacturer/distributor		
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	Adequate	
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.	N/A	

Revised (SN 0017):

(b) (4)

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ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

All of the deficiencies noted above have been satisfactorily resolved. The prescribing information (PI) submitted on July 14, 2021 (SN 0016) is accurate, complete and complies with the requirements under 21 CFR 201. The container (vial) and carton labels as submitted on July 16, 2021 (SN 0017) are likewise accurate, complete and comply with the requirements under 21 CFR 201. From the ONDP perspective, this application is deemed ready for approval in its present form per 314.125(b)(8).

Primary Labeling Assessor Name and Date:

Mark R. Seggel, Ph.D.
Chemist
OPQ/ONDP/DNDPII/Br4

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Wendy Wilson-Lee, Ph.D.
Division Director
OPQ/ONDP/DNDPII

Mark Seggel

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Date: 7/30/2021 09:15:08AM
GUID: 507572b5000036176969356148025bae

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 7/30/2021 09:44:13AM
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