CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215499Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 215499
Assessment #1

Drug Product Name	**APRETUDE**
Dosage Form	**Cabotegravir extended release suspension**
Strength	200 mg/mL
Route of Administration	IM
Rx/OTC Dispensed	Rx
Applicant	Viiv Healthcare Company
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (SD #0002, Rolling submission 2)	05/27/2021	All
Amendment	08/11/2021	Quality/Response to IR

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Kabir Shahjahan	Paresma Patel
Drug Product & Labeling	Peter Guerrieri	David Claffey
Manufacturing	Jin Lee	Yiwei Li
Biopharmaceutics	Gerlie Gieser	Elsbeth Chikhale
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	Peter Guerrieri	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. **RELATED/SUPPORTING DOCUMENTS: Refer to the reviews for the cross-referenced approved NDA 212888.**

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ) at this time. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama 09/14/2021.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The proposed product (APRETUDE®) is indicated for the pre-exposure prophylaxis of HIV infection (PrEP). The majority of the CMC information in NDA 215499 was cross-referenced to NDA 212888 (CABENUVA®), which was approved for the treatment of HIV-1. CABENUVA® is supplied as a kit containing single-dose vials of rilpivirine and cabotegravir, two syringes, two 23 gauge 1.5 in needles, two vial adapters and labels. The CABENUVA® kit contains either 400 mg/2mL (200 mg/mL) or 600 mg/3mL (200 mg/mL) of cabotegravir in a single-dose vial.

APRETUDE® is provided as a single strength: 600 mg/3 mL (200 mg/mL) of cabotegravir and is not co-packaged with rilpivirine. APRETUDE® will be supplied with the cabotegravir vial co-packaged with one vial adaptor, one 5- mL syringe and one 23 gauge 1.5 in needle.

The drug product formulation information and specification are the same in both this NDA and NDA 212888 for the 600 mg/3 mL strength. The manufacturer information in this NDA was also cross-referenced to NDA

212888. As described above, the kit is slightly different because it doesn't contain rilpivirine. The device description is contained in 3.2.R. The proposed shelf life is 36 months, and real-time equivalent long-term stability results were provided and adequately support the 36 month period. Therefore, the 36 month shelf life is granted.

Proposed Indication(s) including Intended Patient Population	Pre-exposure prophylaxis of HIV Infection in at-risk adults and adolescents
Duration of Treatment	Chronic
Maximum Daily Dose	600 mg
Alternative Methods of Administration	None.

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance information in NDA 215499 is cross-referenced to NDA 212888. The CMC information on the drug substance cabotegravir was submitted in the approved NDA 212888 application and found to be adequate. Refer to the DS review for approved NDA 212888, review #01, dated 10-31-2019.

The only API information submitted to NDA 215499 was the current API spec (which was referenced to NDA 212888) and the batch analysis of the drug substance batches used in the clinical trial to support NDA 215499. The drug substance specification provided in the NDA 215499 is consistent with the DS cabotegravir specification in the cross-referenced approved NDA 212888. The batch analysis data for batches used in the clinical studies for NDA 215499 conformed to the proposed specifications.

Drug Product: Adequate

APRETUDE® is provided as a single strength: 600 mg/3 mL (200 mg/mL) of cabotegravir, supplied as the cabotegravir vial co-packaged with one vial adaptor, one 5- mL syringe and one 23 gauge 1.5 in needle. The majority of the drug product CMC information in NDA 215499 is referenced to NDA 212888 (CABENUVA®), which was approved for the

treatment of HIV-1. CABENUVA® is supplied as a kit containing single-dose vials of rilpivirine and cabotegravir, two syringes, two 23 gauge 1.5 in needles, two vial adapters and labels. The CABENUVA® kit contains either 400 mg/2mL (200 mg/mL) or 600 mg/3mL (200 mg/mL) of cabotegravir in a single-dose vial; the latter presentation is used in the Apretude product.

The Cabotegravir Injectable Suspension, 600 mg/3mL and associated devices are exactly the same product co-packaged and registered in NDA 212888, with the same manufacturing sites, processes and specifications. Most drug product information was cross-referenced to NDA 212888. The product is a white to light pink, free-flowing suspension packaged in a clear glass vial with a rubber injection stopper and sealed with an aluminum overseal with a removeable plastic cap in a 3-mL presentation.

Aside from the single packaging presentation noted above, the only additional information included and reviewed were additional batch analyses for clinical batches and the 36 month long-term (5°C and 30°C/75% RH) stability data in support of the 36 month proposed shelf life. The stability results support the proposed shelf life of 36 months at a combined room temperature and refrigerated condition of 2°C to 25°C (36°F to 77°F).

Labeling: Adequate

Recommendations have been conveyed to OND for consideration during labeling revisions. For additional details, see Dr. Peter Guerrieri's Labeling Review.

Manufacturing: Adequate

The drug product is a long acting injectable suspension and is manufactured using a (b) (4) The manufacturing process consists of the (b) (4) (b) (4)

Documentation required in evaluating manufacturing process and facility were submitted in NDA 212888 (FDA-approved in 1/21/2021) and cross-referenced in this NDA. The application is different from NDA 212888 in that the single-use vial is not co-packaged with Rilpivirine 300 mg/mL suspension for injection single-use vial. Also, only one strength (3 mL package (600 mg) at 200 mg API /mL vs. N212888 has 2 mL and 3 mL packages) is proposed in this NDA. Other than the above differences, the proposed manufacturing process and facilities for N215499 are identical to those for NDA 212888. Assessment was performed by cross-referencing relevant documents submitted in N212888 and the corresponding OPMA reviews.

The proposed commercial batch size of (b) (4) L is the same as the registration batch. The overall yields of the registration batches are found acceptable. The drug product is packaged in a clear glass vial with a rubber stopper and sealed with an aluminum overseal with a removable plastic, orange cap. The final kit contains the drug product and one each of single use adapter, syringe (5-mL) and needle (23 gauge and 1.5-inch), which is assembled at the Glaxo Operations UK Limited site (FEI: 3002807078).

One important issue explored during the review of NDA 212888 was (b) (4) In the second review cycle of NDA 212888, the (b) (4) (b) (4) (b) (4) testing, and manufactured three additional commercial scale PQ batches. No further outstanding issue is noted in this NDA in the manufacturing process to support commercial scale manufacturing.

Drug product manufacturing facility (Glaxo Operations UK Limited facility, FEI 3002807078) was downgraded from OAI to VAI as a result of the very relevant PAI in 9/2019, and currently has acceptable profile and GMP compliance status. Drug substance manufacturing facility (Glaxo Wellcome Manufacturing, FEI 3002807079) was approved for the subject API in 6/2019 to support N212888 and currently GMP compliant. All other testing sites and the (b) (4) ((b) (4)) have currently acceptable profiles and GMP compliance status.

Based on the acceptable facility status and adequate manufacturing process control strategies, this NDA is deemed approvable.

Biopharmaceutics: Adequate

The drug product (cabotegravir extended release/ER injectable suspension in single dose vial) evaluated in the pivotal clinical trials and included in the proposed to-be-marketed APRETUDE® Kit is the same as the 600 mg/3 mL (200 mg/mL, 3 mL) cabotegravir ER injectable suspension component of the FDA approved/commercially available CABENUVA® Kit (NDA 212888) owned by the same Applicant and cross-referenced in the current NDA. Thus, formulation bridging studies are not needed to support approval of NDA 215499 of APRETUDE for the HIV-1 PrEP indication.

Based on the provided dissolution data at the time of batch release, the APRETUDE® clinical lots used in pivotal Phase 2b/3 or Phase 3 Studies HPTN-083 and HPTN-084 conformed to the in vitro cabotegravir drug release specifications that were previously approved for the cross-referenced NDA 212888 for CABENUVA®.

Microbiology: Adequate

The drug product is packaged in a kit with components. The components are purchased as sterile. The Cabotegravir drug product is (b) (4) All manufacturing and sterility assurance information is cross-referenced to approved NDA 212888 for CABENUVA®.

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

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BIOPHARMACEUTICS MEMORANDUM TO FILE	
NDA Number	215499
Type of Submission	505(b)(1) NDA
Drug Product **Route of Administration/ Proposed Dosage** (after oral lead-in phase for 1 month)	APRETUDE® (cabotegravir extended release (ER) injectable suspension, 600 mg/3 mL For intramuscular (gluteal) injection; 600 mg/3 mL injection at Months 1 and 2 and every 2 months thereafter
Applicant	ViiV Healthcare Company
Submission Dates	SDN-1 (4/30/2021); SDN-2 (5/27/2021)
Date of Memo	6/7/2021
Biopharmaceutics Consult Reviewers	Gerlie Gieser, Ph.D. (primary) Elsbeth Chikhale, Ph.D. (secondary)
RECOMMENDATION	***Adequate***

EXECUTIVE SUMMARY

The drug product (cabotegravir extended release/ER injectable suspension in single dose vial) evaluated in the pivotal clinical trials and included in the proposed to-be-marketed APRETUDE® Kit is the same as the 600 mg/3 mL (200 mg/mL, 3 mL) cabotegravir ER injectable suspension component of the FDA approved/commercially available CABENUVA® Kit (NDA 212888) owned by the same Applicant and cross-referenced in the current NDA. Thus, formulation bridging studies are not needed to support approval of NDA 215499 of APRETUDE for the HIV-1 PrEP indication.

Based on the provided dissolution data at the time of batch release, the APRETUDE® clinical lots used in pivotal Phase 2b/3 or Phase 3 Studies HPTN-083 and HPTN-084 conformed to the *in vitro* cabotegravir drug release specifications that were previously approved for the cross-referenced NDA 212888 for CABENUVA®.

BIOPHARMACEUTICS REVIEW

Background:

On 1/21/2021, NDA 212888 of CABENUVA®, a co-packaging of cabotegravir suspension long-acting injection/LAI (200 mg/mL) and rilpivirine suspension LAI (300 mg/mL), was approved for the treatment of HIV-1 infection. CABENUVA is commercially available as a kit consisting of two single dose vials containing either 2 mL or 3 mL suspensions of cabotegravir/CAB LAI and rilpirivine/RPV LAI (for intramuscular use) along with syringes, syringe adaptors and needles.

Purpose of the Current Submission:

This 505(b)(1) NDA 215499 seeks the approval of APRETUDE® (cabotegravir suspension (b) (4) injection/ (b) (4) for pre-exposure prophylaxis/PrEP of HIV-1. Per the Applicant, the CAB LAI for PrEP formulation/process/manufacturing sites/controls are *exactly the same* as those for the cabotegravir suspension LAI (200 mg/m; 3 mL) component of CABENUVA® (CAB (b) (4) + RPV (b) (4) Like CABENUVA, the APRETUDE Kit will also come with sterile devices needed for intramuscular

administration of the drug product.

The clinical program of CAB LAI for PrEP of HIV-1 infection in adults and adolescents includes two ongoing Phase 3 studies HPTN-083 and HPTN-084. Per the Applicant, the proposed commercial formulation of CAB LAI (as well as commercial CAB 30 mg oral tablets) was used in the Phase 3 Studies for HIV-1 Treatment and PrEP. Thus, no new Biopharmaceutics studies were conducted to support approval of CAB LAI for PrEP.

In SDN-2 (Delivery 2 of 3; dated 5/27/2021) of this Rolling NDA of APRETUDE® for PrEP, some CMC information is incorporated by cross-reference from the cabotegravir drug substance and cabotegravir drug product (as well as devices information) sections of previously approved original NDA 212888 and supplements of CABENUVA® for the HIV-1 treatment indication. Additionally, the batch numbers (and batch release data for some) of the CAB LAI batches evaluated in the nonclinical and clinical studies (including HPTN-083 and HPTN-084) conducted to support registration of APRETUDE for PrEP were provided in 3.2.P.5.4 Batch Analyses. Note that the third and final delivery of the rolling NDA will include the clinical study report of Phase 3 Study HPTN-084.

Focus of the Biopharmaceutics Review:
The CMC information in SDN-2 of NDA 215499 was assessed to confirm/ascertain whether the clinical and the proposed to-be-marketed drug product APRETUDE® (CAB for PrEP) is the same drug product as (and conforms to the approved drug release specifications for) the cabotegravir extended release suspension component of CABENUVA®.

Biopharmaceutics Reviewer Assessment (Not for the Applicant):

1. A comparison of the documents in Module 3 (CMC) of NDA 215499 for APRETUDE® and NDA 212888 for CABENUVA® indicates that the proposed drug product (APRETUDE) is the same as the 3 mL cabotegravir suspension component of the approved CABENUVA Kit. Specifically, one of the cabotegravir extended release suspension clinical lots (i.e., Batch 182409720) included in 3.2.P.5.4 Batch Analysis of NDA 215499 (APRETUDE for PrEP) and used in Phase 3 Study HPTN-084 appears to have also been used in a Phase 3 clinical study (FLAIR) which supported approval of CABENUVA for the treatment of HIV-1 infections. Additionally, four other drug product lots (i.e., 192413788, 192413267, 192413899, 202418025) included in 3.2.P.5.4 Batch Analysis of NDA 215499 (APRETUDE) were used in Phase 3 Study HPTN-083, whereas two other CAB LAI batches (Lots 192413897 and 192413900) were used in Phase 3 Study HPTN-084.
2. Based on the available *in vitro* dissolution data for five clinical trial lots of cabotegravir ER suspension used in the two pivotal Phase 3 clinical studies, at the time of batch release, the CAB LAI lots conformed to the cabotegravir *in vitro* drug release specifications previously approved for the cross-referenced NDA of CABENUVA® (refer to excerpted table in the Review Appendix), which would be in line with the Applicant's claim that the "commercial" CAB LAI lots were used in the PrEP studies. Refer also to the Biopharmaceutics Review of the original NDA 212888 for the approved *in vitro* drug release QC specifications [USP Apparatus 2 (paddle) at 20 rpm; 1000 mL of 0.5% CTAB in 140 mM McIlvaine Buffer, pH 7.4; 37 °C; 250 µL suspension from each vial; Q = (b)(4)% at 45 min] of the CABENUVA Kit's cabotegravir extended release suspension component.

Comments for the Applicant:
None

APPEARS THIS WAY ON ORIGINAL

REVIEW APPENDIX

Table 5 Batch Analysis Data for Batches of Cabotegravir Injectable Suspension Used in Clinical Studies (Cont'd)

(b) (4)

[redacted]

Reviewer Note (footnote 6 of table):

Procedure C is the dissolution method for cabotegravir ER injectable suspension approved in referenced NDA 212888.

Gerlie Gieser

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Elsbeth Chikhale

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	215499
Assessment Cycle Number	01
Drug Product Name/ Strength	APRETUDE (Cabotegravir) 200 mg/mL (600 mg in 3 mL)
Route of Administration	Intramuscular injection
Applicant Name	ViiV Healthcare Company
Therapeutic Classification/ OND Division	CDER/OND/OID/DAV
Manufacturing Site	Cabotegravir: Glaxo Operations UK Limited (trading as Glaxo Wellcome Operations) Harmire Road Barnard Castle County Durham DL128DT UK
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
Original submission (SD#0002, Rolling Submission 2)	5/27/2021

List Submissions being assessed: See table above

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

Remarks: The drug product is packaged in a kit with components. The components are purchased as sterile. The Cabotegravir drug product is (b) (4)

Cabotegravir is an extended release long-acting suspension intended for pre-exposure prophylaxis of HIV infection. All manufacturing and sterility assurance information is cross-referenced to approved NDA 212888 for CABENUVA®.

Concise Description of Outstanding Issues: N/A

Supporting Documents:

- Microbiology review N212888.docx (adequate) dated 10/23/2019 for all manufacturing and sterility assurance information.

(b) (4)

[redacted]

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Sallie Crenshaw

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Bethanie Lee

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	
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.	Adequate	
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	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
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)	Adequate	Adequate. The in-use conditions are supported by in-use stability results. The previously approved Cabenuva product included the Cabotegravir suspension as a co-packaged vial. The storage condition for the Cabenuva product is refrigerated (2°C to 8°C). To avoid confusion with providers who may want to store Apretude together with Cabenuva, a combined room temperature and refrigerated storage statement is recommended as follows: "Store at 2°C to 25°C (36°F to 77°F). (b) (4) exposure up to 30°C (86°F) permitted." Instructions for bringing the vial to room temperature before use, if the pack was stored in the refrigerator, are included in section 2.7 of the PI and in the Instructions for Use.
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 parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever*	Adequate	

solution and container permit"		
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 11).	N/A	
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 *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	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	
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 type terms include pharmacy bulk package and imaging bulk package.	Adequate	Dosage form is appropriately described as single-dose.

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
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 Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. 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.	Adequate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	Adequate	
Pharmacological/Therapeutic class	Adequate	
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)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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	
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	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	APRETUDE is described as a kit containing the vial of cabotegravir extended-release injection, syringe, vial adapter and needle for intramuscular injection.
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
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.	Adequate	Dosage form is appropriately described as 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.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	Adequate. The shelf life and in-use conditions are supported by stability results.

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

Item	**Items in Proposed Labeling** (choose "Adequate", "Inadequate", or "N/A")	**Assessor's Comments** (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Adequate. The shelf life and in-use conditions are supported by stability results. The previously approved Cabenuva product included the Cabotegravir suspension as a co-packaged vial. The storage condition for the Cabenuva product is refrigerated (2°C to 8°C). To avoid confusion with providers who may want to store Apretude together with Cabenuva, a combined room temperature and refrigerated storage statement is recommended as follows: "Store at 2°C to 25°C (36°F to 77°F). (b) (4)

		exposure up to 30°C (86°F) permitted."
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	Adequate	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):
The product is to be administered by healthcare professionals only. The IFU was reviewed by DMEPA.

Instructions for bringing the vial to room temperature before use, if the pack was stored in the refrigerator, are included in section 2.7 of the PI and in the Instructions for Use.

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Adequate	The previously approved Cabenuva product included the Cabotegravir suspension as a co-packaged vial. The storage condition for the Cabenuva product is refrigerated (2°C to 8°C). To avoid confusion with providers who may want to store Apretude together with Cabenuva, a combined room temperature and refrigerated storage statement is recommended as follows: "Store at 2°C to 25°C (36°F to 77°F). (b) (4) exposure up to 30°C (86°F) permitted."
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 differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	The statement, "for gluteal intramuscular use only" is included.
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	The previously approved Cabenuva product included the Cabotegravir suspension as a co-packaged vial. The storage condition for the Cabenuva product is refrigerated (2°C to 8°C). To avoid confusion with providers who may want to store Apretude together with Cabenuva, a combined room temperature and refrigerated storage statement will be recommended. Recommended edit: Update the storage statement on the container label to read "Store at 2°C to 25°C (36°F to 77°F). See insert."
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, and these products require a "Not for direct infusion" statement.	Adequate	

For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
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.	Adequate	

Assessment of Carton and Container Labeling: *Adequate.*

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

ITEMS FOR ADDITIONAL ASSESSMENT

Requested edits to be conveyed to OND:

Update the storage statement on the container label to read:

"Store at 2°C to 25°C (36°F to 77°F). See insert."

Overall Assessment and Recommendation:

Recommend edits will be provided to OND.

Primary Labeling Assessor Name and Date: Pete Guerrieri, PhD

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

Peter Guerrieri

Digitally signed by Peter Guerrieri
Date: 11/18/2021 11:27:20AM
GUID: 54eb8ba100062ea99cbaab7c64143df3

David Claffey

Digitally signed by David Claffey
Date: 11/18/2021 03:51:23PM
GUID: 508da71e00029e20b201195abff380c2

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – GLASS LUER PRE-FILLED SYRINGES

Date	8/27/2021		
To:	Shamika Brooks, RPM		
Requesting Center/Office	CDER/OPQ	**Clinical Review Division**	DNDPI/NDPB2
From	Janice Ferguson, RN, BSN, CRNI OPEQ/OHT3/DHT3C		
Through (Team)	David Wolloscheck, Acting Team Leader OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Payal Patel, Acting Director OPEQ/OHT3/DHT3C		
Subject	ICCR: **00722738** ICC: **2100482** Submission: **NDA215499** Sponsor: **ViiV Healthcare** Drug/Biologic: **APRETUDE (Cabotegravir)** Indications for Use: **Indicated for at risk individuals weighing at least 35 kg for Pre-Exposure Prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection.**		
Recommendation	**Final Recommendation: 10/28/2021** ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with the following Post-Market Requirements/Commitments, ☐ Device Constituent Parts of the Combination Product are Not Approvable with the following CR Deficiencies		
	Comments to Review Team: **The device constituent parts of NDA215499 are identical to those reviewed in NDA212888**. The sponsor has cross-referenced NDA212888 for all device verification, validation, and risk management activities. **The co-packaged components found within this submission were reviewed under ICC1900382 and found to be APPROVABLE.**		
	PMC/PMR or CR Deficiencies: **NONE**		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (*Optional)**
APPEARS THIS WAY ON ORIGINAL		

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA215499
Sponsor	ViiV Healthcare
Drug/Biologic	Apretude (Cabotegravir) Injectable
Indications for Use	Indicated for at risk individuals weighing at least 35 kg for Pre-Exposure Prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection.
Device Constituent	Combo Pack (Vial adapter, 5mL syringe and Safety Needle)
Related Files	NDA212888

Important Dates	
Filing	NA
74-Day Letter	NA
Midcycle Meeting/IRs due	9/15/2021
Final Lead Device Review Memo Due	10/28/2021
PDUFA	12/10/2021

2. MATERIALS REVIEWED

Materials Reviewed		
NDA 212888		
Sequence 0001	1.4.4 3.2R	Cross-reference to Previously submitted information Attachment Devices
Sequence 0033	1.11.1	Information Amendment
NDA 215499		
Sequence 0002	1.14.1.1 3.2.A 3.2.R 3.2.R	Labeling Appendices Cross-Referenced Statement Regional Information Cross-Reference Statement Medical Devices
Sequence 0015	1.11.1	CMC Response to Questions 22 Jul2021

3. PURPOSE

This review provides an assessment of the device constituent part of the device constituent components, co-packaged with APRETUDE (cabotegravir extended-release injectable suspension) for intramuscular use. The Combo Pack consists of a vial adapter, 5 mL syringe, and a safety needle. APRETUDE is an HIV-1 integrase strand transfer inhibitor (INSTI)

Consult Request: The co-pack is different from NDA 212888- but the main difference is that it is no longer co-packaged with rilpivirine. The co-pack for NDA 215499 includes cabotegravir (3mL) and the same 5 mL syringe and 23-gauge 1.5-inch safety needle covered in the CDRH review of NDA 212888. The only change was for the manufacturer of the vial adapter. There's the file in 3.2.R labeled "medical devices." Please review this file.

NOTE: The sponsor confirmed via an Information Request dated 7/29/2021 that the device constituent parts of this current submission NDA215499 are the same as those for NDA212888. This includes one each: vial adapter, 5 mL syringe and safety needle.
Per an email dated 8/23/2021 from CDER [Peter Guerrieri] the request for device evaluation was withdrawn. A request was made by David Claffey to provide a quick memo or email indicating that the components are acceptable as they are the same as NDA212888.

This review **WILL** cover the following review areas:

☒ Device constituent performance[1]

This review will **NOT** cover the following review areas:

☒CDRH Quality Systems Assessment / Facilities*
☒ Drug product/container closure performance
☒ Biocompatibility
☒ Sterility
☒ Human factors
☒ Control Strategy

*It was determined that a device quality systems / facilities assessment is not required for this product because the product is not an emergency (i.e., life-saving, and essential[2]) treatment that are administered by non-health care professionals.

4. DEVICE DESCRIPTION

NDA 215499 - 510(k) numbers

	Tradename and Identifier	510(k) Reference
Vial Adapter	(b) (4)	
Syringe		
Safety Needle		

[1] The scope of this review will be limited to the device constituent performance in accordance with FDA recognized versions of ISO 80369-7, ISO 594-1, ISO 594-2 and FDA guidance *Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices*. For a PFS with a luer connector, the review will be limited to luer connectivity performance requirements and will not cover functions of the primary container/simple syringe (dose accuracy/container content, break loose force, glide force, cap removal) and their control strategy. There are no control strategy considerations for luer connectivity. Additional review may be warranted for any co-packaged devices, as applicable.

[2] Examples of emergency, life-saving and essential treatments include those used for conditions such as anaphylaxis or cardiac arrest and others in which failure of drug delivery may expose the patient to the reasonable likelihood of serious injury or death.

NDA 212888 510(k) numbers

APPEARS THIS WAY ON ORIGINAL

	Tradename and Identifier	Description	Material of Construction (Product Contact)	Packaging	Manufacturer	Device Classification	510(k) Reference	Reference
Vial Adapter	[redacted]						(b) (4)	3.1.1
Syringe								3.1.2
Safety Needle								3.1.3

Reviewer Comment:
An IR was sent to the sponsor on 7/22/2021, confirming that the device constituent parts for NDA215499 are identical to those that were used in NDA212888. *This was conveyed to CDER.*

4.1 Picture of Final device Presentation

Side by side comparison of Device components

NDA215499	NDA212888
[redacted]	(b) (4)

Reviewer Comment:
The 510(k) numbers and the device constituent parts of NDA215499 are identical to those of NDA212888.

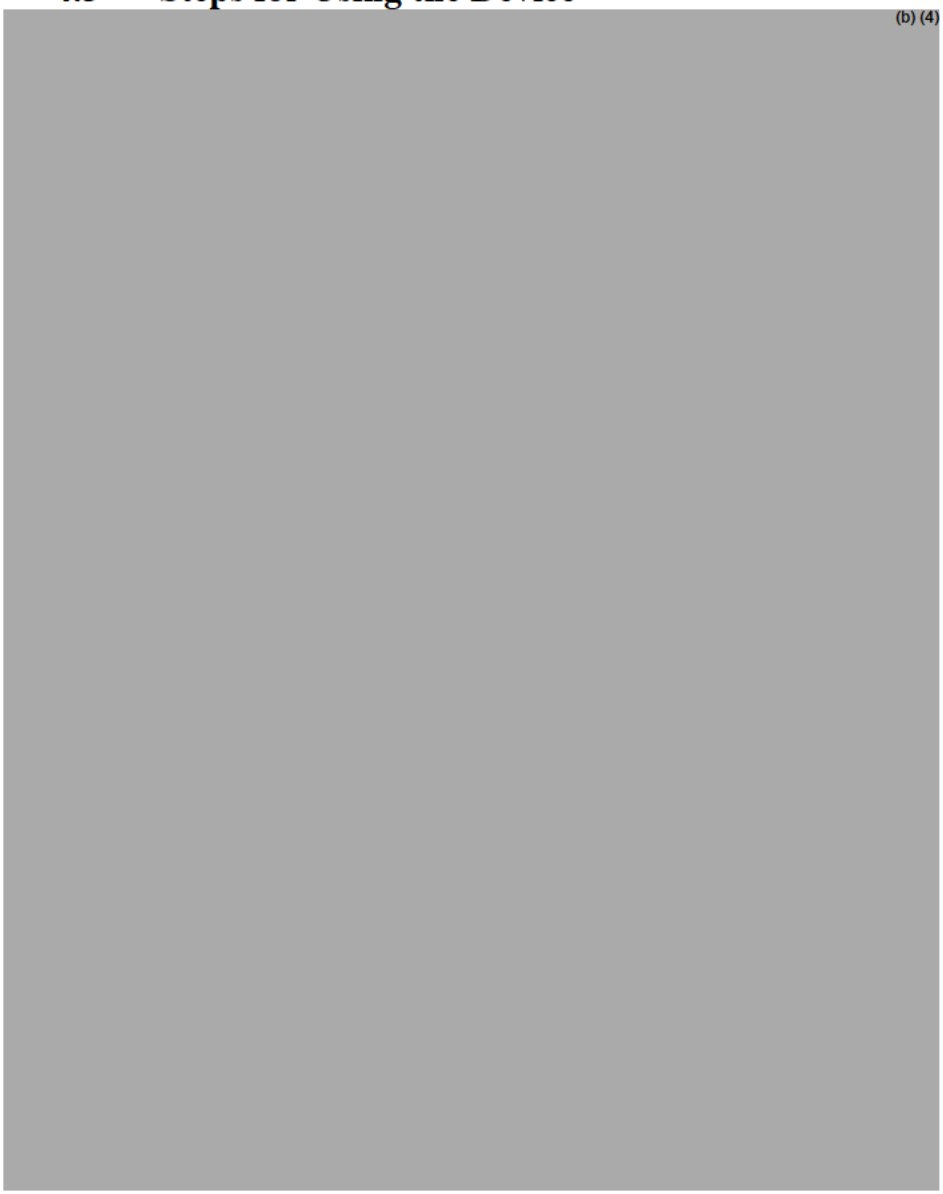
Representative Drawings

Reviewer Comment:
Information regarding the device description was referenced and found in NDA 212888. The sponsor provided within the information request dated 7/29/2021 that the device constituents parts of the Combo Pack for NDA 215499 are the same as those used in the Combo Pack for NDA 212888. The only difference is that only one device of each type is provided for administration of a single drug. (Two of each device was provided for NDA 212888 as it was a two drug Combo Pack).
Documentation supporting the validation of the co-packaged components was provided in the HF validation.
The device is adequately described and is acceptable.

4.2 Design Requirements

Requirement	Describe
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Healthcare professionals
Dosage	600 mg (3 mL) given 1 month apart for 2 consecutive months then, 600 mg every 2 months
Injection Site	Ventrogluteal
Injection tissue	Intramuscular

4.3 Steps for Using the Device



Reviewer Comment:
The instructions for use are identical to those provided in NDA 212888.
This is acceptable

5. DEVICE PERFORMANCE REVIEW

Design Functional Requirements

Design Input	Design Output	Verification Method	Results/Deviations	Adequately Verified Y/N	Validated though Clinical, HF or other	Adequately Validated Y/N
Dose Accuracy	Aligned to drug product specification for extractable volume	Compliance to ISO 7886-1	Delivered Volume contents from syringe 3 mL	Y	Y-Human Factors	Y
Absence of Leakage	Aligned to drug product specification for extractable volume	Compliance to ISO 80369-7	No leakage	Y	Y-Human Factors	Y
Vial, Vial Adaptor and Needle Compatibility	Aligned to drug product specification for extractable volume	Compliance to ISO 80369-7	All device constituent parts are compatible	Y	Y-Human Factors	Y
Injection force	(b) (4) (b) (4) N (Max Value)	Compliance to ISO 7886-1	(b) (4) N	Y	Y-Human Factors	Y

Essential Performance Requirement Evaluation

Table 4 Summary of Device Verification Bench Test Results APPEARS THIS WAY ON ORIGINAL

Test	Acceptance Criteria	Sample Size (# of units)	Mean Result	Minimum - Maximum (Std. Deviation)	Overall Result
Leakage test for syringe-needle connection[1] (mm)	The plunger displacement remains less than or equal to (b) (4) mm when subjected to an injection force of (b) (4) N after attachment of the safety needle to the syringe.	30	0.040	0.015 - 0.066 (0.020)	Pass
Vial adapter attachment/detachment force (N)	The force required to attach the vial adapter onto the vial shall not exceed (b) (4) N.	30	25.62	22.23 - 28.49 (1.73)	Pass
	The force required to disconnect the vial adapter from the vial shall be greater than (b) (4) N when applied axially.	30	16.15	13.08 - 22.61 (1.97)	Pass
Unscrewing torque test (Nm)	The unscrewing torque required to disconnect the vial adapter from the syringe shall be equal to or greater than (b) (4) Nm as per ISO 80369.	30	0.060	0.042 - 0.069 (0.006)	Pass
Separation force test (N)	The force required to separate the syringe from the vial adapter in the axial direction shall exceed (b) (4) N as per ISO 80369-20.	30	165 N	144 – 195 (13)	Pass
Stress cracking test[1]	The syringe to vial adapter connection shall not break or leak when tested according to ISO 80369-20 stress cracking.	30	No visual cracks observed after 48 hours	N/A	Pass
Unscrewing torque test (Nm)	The unscrewing torque required to disconnect the safety needle from the syringe shall be equal to or greater than (b) (4) Nm as per ISO 80369.	30	0.074	0.055 - 0.089 (0.009)	Pass
Separation force test (N)	The force required to separate the syringe from the needle shall exceed (b) (4) N as per ISO 80369-20.	30	58.8	51.7 - 65.3 (3.6)	Pass
Stress cracking test[1]	The syringe to needle connection shall not break or leak when tested according to ISO 80369-20 stress cracking.	30	No visual cracks observed after 48 hours	N/A	Pass

Notes:
1. Results of time zero points of functional stability tests are included.
N/A Not applicable

Table 5 Stress Cracking Test and Leakage Test Results Following Storage at 25°C/60% RH APPEARS THIS WAY ON ORIGINAL

Test	Acceptance Criteria	Sample Size (# of units)	Timepoint (months)			
			Initial	1.5	3	6
Syringe to Vial Adapter connection - Stress Cracking	No visual cracks shall be visible 48 hours after stress crack testing	30	Pass	Pass	Pass	Pass
Syringe to Needle connection - Stress Cracking	No visual cracks shall be visible 48 hours after stress crack testing	30	Pass	Pass	Pass	Pass
Syringe to Needle connection - Leakage test in use condition (simulation of injection)	Plunger displacement (b) (4) mm after 48 hours	30	Pass	Pass	Pass	Pass

Table 6 Injectability Force for Rilpivirine Extended-release Suspension for Injection Following Storage at 25°C/60% RH

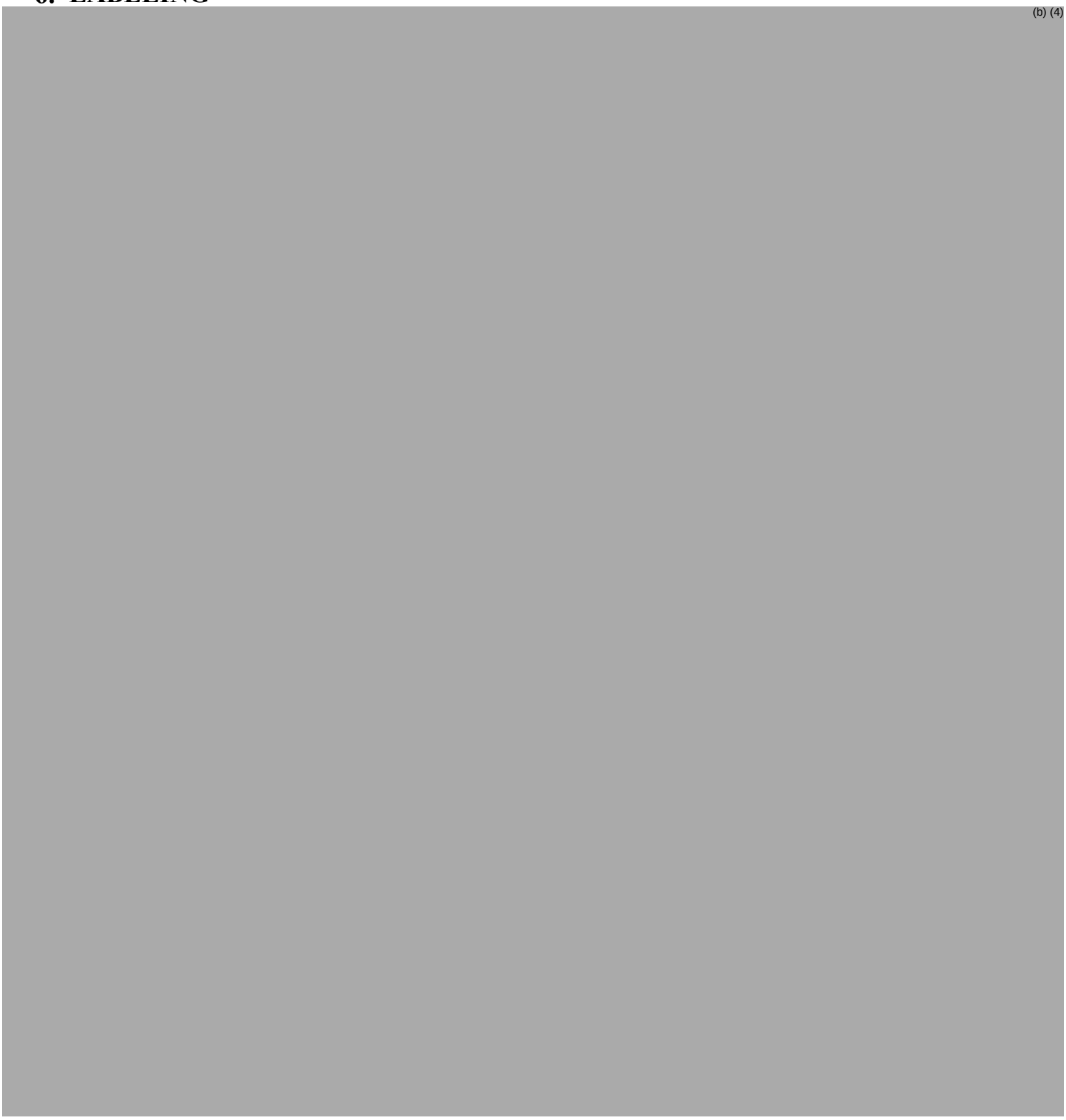
Test	Acceptance Criteria	Sample Size (# of units)	Timepoint (months)	Mean Result	Minimum-Maximum (Std. Deviation)	Overall Result
Injection force (N) 3-mL fill presentation	Average injection force of each measurement (b) (4)	30	Initial	16.2	15.1 – 17.6 (0.8)	Pass
			1.5	15.2	14.4 – 16.6 (0.6)	Pass
			3	16.1	15.0 – 17.4 (0.6)	Pass
			6	14.9	13.5 – 16.0 (0.7)	Pass

APPEARS THIS WAY ON ORIGINAL

Reviewer Comments:
Information regarding the device performance was referenced and found in NDA 212888. Appropriate ISO standards were utilized. The sponsor identified appropriate essential performance standards and provided design verification testing, complete and adequate test reports. Individual device components were tested and cleared within their 510k submissions. *This is acceptable.*

6. LABELING

(b) (4)



Reviewer Comment:
The drug product is to be administered by a healthcare professional. *The labeling and instructions for use are adequate*. [Instructions for use found in 4.3 Steps for use of the device].

<<END OF REVIEW>>

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PETER P GUERRIERI
11/19/2021 10:50:28 AM