CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213983Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 213983
Assessment #1

Drug Product Name	Dolutegravir
Dosage Form	Tablets for Oral Suspension
Strength	5 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	ViiV
US agent, if applicable	GSK

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Dec 12, 2019	All
Amendment	Jan 21, 2020	Quality
Amendment	Feb 6, 2020	Quality
Amendment	Feb 25, 2020	Quality
Amendment	Mar 19, 2020	Quality
Amendment	Mar 20, 2020	Quality
Amendment	Apr 24, 2020	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Soumya (Shomo) Mitra	Ali Al Hakim
Drug Product & Labeling	Soumya (Shomo) Mitra	Thomas Oliver (DP) Stephen Miller (Labeling)
Manufacturing	Naveen Kanthamneni	Bo Jiang
Biopharmaceutics	Gerlie Gieser	Elsbeth Chikhale
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	Stephen Miller	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)		Adeq.	See DP review	
	III			Adeq.	See DP review	
	III & IV			Adeq	See DP review	

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

Document	Application Number	Description
NDA	204790	DS information
IND	75382	Clinical studies

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH-ODE	NA			
CDRH-OC	NA			
Clinical	NA			
Other				

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

NDA 213983 is recommended for APPROVAL from the product quality perspective.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

TRADEMARK* (dolutegravir) tablets for oral suspension (TOS), 5 mg, were developed to provide appropriate dosing for pediatric patients, in addition to what is available with the previously-approved 10, 25 and 50 mg tablets. An oral syringe, a dosing cup, and detailed instructions for use are provided with the bottle of 60 tablets, to allow administration of the oral suspension to infants.

* Two trademarks are currently under evaluation from the patient safety perspective: (b) (4)" and "TIVICAY PD".

Proposed Indication(s) including Intended Patient Population	In combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and in pediatric patients aged at least 4 weeks and weighing at least 3 kg
Duration of Treatment	Chronic
Maximum Daily Dose	5 – 30 mg/day of TOS depending on body weight; one 50 mg (conventional) tablet is the adult dose
Alternative Methods of Administration	The tablets for oral suspension can be swallowed intact or dispersed in water

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance information for dolutegravir sodium is provided by cross-reference to the approved NDA 204790 for TIVICAY tablets from ViiV. The current drug substance specifications from NDA 204790 are provided in S.4.1 for the two routes of synthesis ((b) (4) With the exception of several process-specific impurities (NMT (b) (4) %) both specifications (b) (4). Both specifications include particle size control (X_{90} NMT (b) (4) um) and a verification of identity for solid-state form (b) (4) The use of drug substance (b) (4) for manufacture of the tablets for oral suspension is supported by drug product data.

For additional information, see Soumya (Shomo) Mitra's Drug Substance Review, below.

Drug Product: Adequate

Dolutegravir tablets for oral suspension (TOS), 5 mg, are round (6 mm diameter), biconvex, white, film coated tablets, debossed with "SV H7S" on one face and "5" on the other face. Each tablet (5 mg dolutegravir free acid) contains 5.26 mg of dolutegravir sodium salt. The tablets are packed in a white, opaque, round, HDPE bottle with a (b) (4) child resistant closure (CRC) that includes a (b) (4) induction seal liner. Each bottle contains 60 tablets, and one 2 g silica-gel desiccant (b) (4) The tablets are not scored.

A 10 mL oral syringe, a 30 mL dosing cup, and detailed instructions for use are included in the carton. The tablets may be swallowed whole or a dispersion in water can be prepared: 5 mL for (b) (4) tablets and 10 mL for 4-6 tablets. The oral syringe and dosing cup are compliant (b) (4) meet USP <661> "Plastic packaging systems and their materials of construction," and are fit for purpose. The reconstituted suspension was stable for 30 (b) (4) minutes after preparation, and good recovery was demonstrated using the rinse recommended in the labeling.

The formulation uses (b) (4) excipients (b) (4) (b) (4) . The specifications for excipients are adequate. The drug product specification includes attributes appropriate for the TOS dosage form (fineness of dispersion; disintegration) and is acceptable. The theoretical risk for changes in dolutegravir Na solid-state form during DP manufacture has been adequately mitigated. An x-ray powder diffraction study confirmed the presence of (b) (4) (the form in the drug substance) with no evidence of conversion to (b) (4) or (b) (4) forms (April 24, 2020 amendment).

The stability of the drug product is supported by 24 months of data on TOS manufactured at the commercial site and scale ((b) (4) tablets; (b) (4) The studies include the 30°C/75% RH long-term condition. The only trend on stability is a moderate increase in (b) (4), and the data adequately support a 36-month expiration dating period when stored "Below 30°C (86°F)." Secondary stability studies are presented which support the use of drug substance from both routes of synthesis, the commercial cap liner, and the alternate film-coat.

Additionally, the application includes acceptable data from a 24 month study on tablets (b) (4), and (b) (4)-day in-use studies. Established Conditions (EC), proposed in the initial submission, were removed from the NDA (Jan 21, 2020 amendment) and deferred until the final FDA guidance on ICH Q12 has been published.

For additional information, see Soumya (Shomo) Mitra's Drug Product Review, below.

Labeling: Adequate

Recommendations have been conveyed to OND for consideration during labeling revisions. For additional details, see Soumya (Shomo) Mitra's Labeling Review, below.

Manufacturing: Adequate

(b) (4)

The drug substance manufacturing facilities have manufacturing experience with proposed DS and are currently cGMP compliant. The drug product facility has experience with manufacturing solid dosage forms and is currently cGMP compliant. All facilities are currently acceptable, and Overall Manufacturing Inspection Recommendation is "Approve" as of May 4, 2020

For additional details, see Naveen Kanthamneni's Manufacturing Review, below.

Biopharmaceutics: Adequate

The dissolution method and acceptance criterion are both adequate:

- USP Apparatus II (paddle) at 50 rpm, 900 mL of 0.01M Phosphate buffer, pH 6.8
- Q = (b) (4)% at 25 min

The submitted in vitro and in vivo PK data/information are adequate to establish the bridge from the drug product used in the clinical/stability studies to the final proposed to-be-marketed drug product.

The dissolution profiles and other information provided in the Feb 6, 2020 amendment support the manufacture of the TOS using dolutegravir sodium drug substance produced by either the (b) (4) or (b) (4) synthetic processes.

For additional details, see Gerlie Gieser's Biopharmaceutics Review, below.

Microbiology (if applicable): Choose an item.

NA

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations & Comments**
Assay, Stability		**L**	(b) (4)	Acc	
Physical stability (solid state)	Based on dolutegravir (low solubility)	**M**		Acc	
Content uniformity	Based on dolutegravir (b) (4)	**M**		Acc	
Microbial limits	Microbial testing performed if (b) (4)	**L**		Acc	
Dissolution – BCS Class II & IV	Based on low solubility dolutegravir	**M**		Acc	
Patient Use Considerations	Instructions for dispersing are included	**M**		Acc	

D. List of Deficiencies for Complete Response – None / NA

Stephen Miller

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	(b) (4) or TIVICAY PD	Either name is Adequate
Established name(s)	Dolutegravir	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Dispersible tablets for oral suspension, 5 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Tablet is not scored	
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.	N/A	

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		
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)	(b) (4)	Adequate. The Applicant stated not to crush, cut or chew the tablets for oral suspension, but the reason for this statement is unclear. Pediatric patients using the tablet formulation should not swallow more than one tablet at a time to reduce the risk of choking.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Tablets:

10 mg: Each tablet contains 10 mg of dolutegravir (as dolutegravir sodium). Tablets are white, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "10" on the other side.

25 mg: Each tablet contains 25 mg of dolutegravir (as dolutegravir sodium). Tablets are pale yellow, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "25" on the other side.

50 mg: Each tablet contains 50 mg of dolutegravir (as dolutegravir sodium). Tablets are yellow, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "50" on the other side.

Tablets for Oral Suspension:

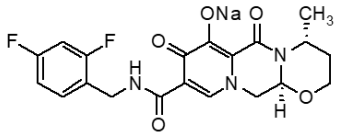
Each tablet contains 5 mg of dolutegravir (as dolutegravir sodium). Tablets are white, round, film-coated, biconvex tablets debossed with “SV H7S” on one side and “5” on the other side.

Item	Information Provided in the NDA	Assessor’s Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	5 mg tablets for oral suspension and previously approved tablets	Adequate
Strength(s) in metric system	Dolutegravir tablets, 5 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Yes Each film-coated tablet contains 5 mg of dolutegravir (as dolutegravir sodium)	Adequate. The description section clarifies whether the strength is based on the active moiety or active ingredient (salt), as per the FDA salt-naming guidance.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	White, round, film-coated, biconvex tablets debossed with “SV H7S” on one side and “5” on the other side	**Revise to:** “White, round, strawberry cream flavored, film-coated, biconvex tablets debossed with “SV H7S” on one side and “5” on the other side” per the CDER Labeling Review Tool.
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 labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	(b) (4) and dolutegravir	Adequate
Dosage form(s) and route(s) of administration	Tablets, Oral	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Equivalency statement: Each (b) (4) tablet for oral suspension contains 5.26 mg of dolutegravir sodium, which is equivalent to 5 mg dolutegravir free acid.	Adequate. Includes the equivalency statement recommended by the CDER Labeling Review Tool and the FDA salt-naming guidance.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	*Inactive ingredients*: calcium sulfate dihydrate, crospovidone, mannitol, microcrystalline cellulose, povidone K29/32, silicified microcrystalline cellulose, sodium starch glycolate, strawberry cream flavor, sucralose, and sodium stearyl fumarate. The tablet film-coating contains hypromellose, polyethylene glycol, and titanium dioxide.	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.	N/A	
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)	N/A	
Pharmacological/ Therapeutic class	HIV-1 integrase strand transfer inhibitor (INSTI) (an antiretroviral agent)	Adequate

Chemical name, structural formula, molecular weight	**Dolutegravir Sodium:** sodium (4*R*,12a*S*)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate ***Mol. Wt.*** 441.36 g/mol 	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	No information included in the PI	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	None	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

TIVICAY tablets, 10 mg, are white, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "10" on the other side. Bottle of 30 tablets with child-resistant closure and containing a desiccant. NDC 49702-226-13.

Store and dispense the 10-mg tablets in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

TIVICAY tablets, 25 mg, are pale yellow, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "25" on the other side. Bottle of 30 tablets with child-resistant closure. NDC 49702-227-13.

TIVICAY tablets, 50 mg, are yellow, round, film-coated, biconvex tablets debossed with “SV 572” on one side and “50” on the other side. Bottle of 30 tablets with child-resistant closure. NDC 49702-228-13.

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

(b) (4) tablets for oral suspension, 5 mg, are white, round, film-coated, biconvex tablets debossed with “SV H7S” on one side and “5” on the other side. Bottle of 60 tablets with child-resistant closure containing a desiccant. Each bottle is packaged with one 30-mL dosing cup and one 10-mL oral dosing syringe with 1-mL gradations. NDC 49702-255-37.

Store (b) (4) tablets for oral suspension below 30°C (86°F). Store and dispense the 5-mg tablets in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablets	Adequate
Strength(s) in metric system	Dolutegravir, 5 mg	Adequate
Available units (e.g., bottles of 100 tablets)	HDPE bottle of 60 tablets with child-resistant closure containing a desiccant. Each bottle is packaged with one 30-mL dosing cup and one 10-mL oral dosing syringe with 1-mL gradations. NDC 49702-255-37.	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Tablets for oral suspension, 5 mg, are white, round, film-coated, biconvex tablets debossed with "SV H7S" on one side and "5" on the other side. NDC 49702-255-37	**Revise to:** "Tablets for oral suspension, 5 mg, are white, round, film-coated, strawberry cream flavored, biconvex tablets debossed with "SV H7S" on one side and "5" on the other side" per the CDER Labeling Review Tool.
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.	N/A	

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

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store (b) (4) tablets for oral suspension below 30°C (86°F). Store and dispense the 5-mg tablets in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.	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."	Warning statement is included in Instructions for Use section: The bottle contains a desiccant (b) (4) . **Do not** remove the desiccant.	Adequate: the desiccant (b) (4) is significantly larger than the tablets for oral suspension.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store (b) (4) tablets for oral suspension below 30°C (86°F). Store and dispense the 5-mg tablets in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.	Adequate per DAV recommendations for anti-HIV drugs demonstrated to be stable at 30°C/75%RH.
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."	N/A	
Include information about child-resistant packaging	Yes. Provided.	Adequate. The supporting child resistant information is submitted in section 3.2.P.7.

1.2.5 Other Sections of Labeling

None

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		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	(b) (4) ViiV Healthcare Research Triangle Park, NC 27709 (b) (4) GlaxoSmithKline Research Triangle Park, NC 27709	Adequate

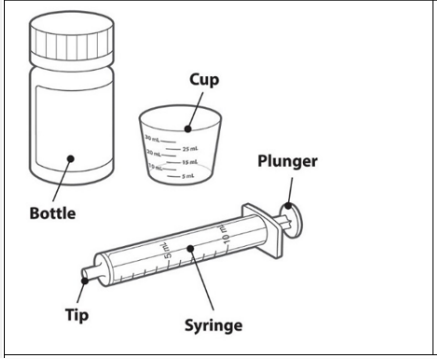
2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling
(Summarized from Medication Guide, Patient Information and Instructions for Use):

Under drug interaction information, the Applicant states that Tivicay should be taken 2 hours before or 6 hours after taking any cation-containing antacids and laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications.

Patient is recommended to use clean drinking water for preparation of dose for infants or a child who cannot swallow the tablets. The Applicant stated not to crush, chew or cut the dispersible tablets, and not to give two (2) doses at the same time. A child can however, swallow the tablets. The following illustration was found in the package for patients, in which the syringe is meant to be used for infants and the plastic cup for preparing medicine for children and for infants:

Your pack contains:



- A bottle containing 60 (b) (4)
- Dosing kit:
  - **Cup:** Use this to prepare and give the medicine to **children.**
  - **Syringe:** Use this to give the medicine to **infants.**

Water volume measurement in the cup: For (b) (4) tablets, 5 mL water volume, and for 4–6 tablets, 10 mL of water volume is recommended for proper dispersion of the tablets. Gentle swirling of the cup for 1–2 minutes is stated to assist in proper dispersion of the medicine without any lumps, and at that time it appears to be a cloudy suspension ready for use. The medicine should be administered within 30 minutes of preparation of the dose. Another 5 mL of water can be used for swirling and administering any residual medicine in the cup to be assured that full recommended dose is administered.
For infants: A syringe is used to draw-up all the medicine by pulling-up the plunger. The tip of the syringe is then placed against the inside of infant's cheek, and the plunger is pushed down to release the dose slowly. As above, another 5 mL of clean drinking water can be used to swirl the cup to collect any residual medicine, then drawing-up in the syringe and administering it to the infant will assure that the infant gets the full dose. After administration of the medicine, it is recommended to wash the cup, syringe and plunger with clean water, properly drying the parts and reassembling for storing, to be ready for the next use.

Storage: All the tablets are to be kept in the original bottle with cap tightly closed and out of reach of children. The bottle contains desiccant (silica-gel) (b) (4)

(b) (4)

All the materials in the package are recommended to be disposed in regular household trash can after all the tablets in the medicine container has been utilized.

Assessment of Instructions for Use, Patient Labeling, *etc.*: Adequate

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

An updated container label was submitted by the Applicant on 04/24/2020 in eCTD 0017 (SDN 17), which included “For Pediatric Dosing” and modified the proprietary name to Tivicay PD, as shown below. There is no concern from product quality perspective on this updated label from the Applicant.

3.2 Carton Labeling

An updated carton label was submitted by the Applicant on 04/24/2020 in eCTD 0017 (SDN 17), which included “For Pediatric Dosing” as shown below. There is no concern from product quality perspective on this updated carton label from the Applicant. Further review on these updated labels are ongoing with DMEPA and Clinical review staff from a patient safety perspective.

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	(b) (4) Dolutegravir Tablets for Oral Suspension (as modified after FDA recommendation)	No concerns from the OPQ perspective. DMEPA reviewer will determine adequacy of font size and prominence. From OPQ Perspective: "(b) (4) (dolutegravir) tablets for oral suspension" is preferred and was discussed with DMEPA.
Dosage strength	Dolutegravir 5 mg	Adequate
Route of administration	Oral	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Yes Each tablet contains 5 mg of dolutegravir equivalent to 5.26 mg of dolutegravir sodium.	Adequate
Net contents (e.g. tablet count)	60 tablets	Adequate
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	NDC 49702-255-37	Adequate
Lot number and expiration date	Yes, provided	Adequate Expiration date is provided on both the container and carton labels
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	**Keep out of reach of children.** Store below 30°C (86°F). Store in the original package to protect from moisture. Keep the bottle tightly closed. Do not remove desiccant.	Adequate Adequacy of container labels from the perspective of pharmacy (e.g., space for BUD) is evaluated by DMEPA.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
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	Alcohol not present	
Bar code	Yes. States NDC No. 49702-255-37 on carton label, Container label states the following: N00349702255371	Adequate. NDC number is stated in the barcodes

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	(b) (4): ViiV Healthcare, RTP, NC 27709 (b) (4) GlaxoSmithKline RTP, NC 27709	Adequate
Medication Guide (if applicable)	Provided in PI	
No text on Ferrule and Cap overseal	None	
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.	Not a compendial product	
And others, if space is available	None	

Assessment of Carton and Container Labeling: ***Adequate***
The bottle label complies with all regulatory requirements from a CMC perspective.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."
No deficiencies

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

Adequate from CMC perspective. Recommendations for consideration during labeling negotiations are noted in this review and have been conveyed to OND.

Primary Labeling Assessor Name and Date:

Soumya Mitra, PhD. OPQ/ONDP/DNDAPI/Branch 1

Dated: 05/05/2020

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

Stephen Miller, PhD. OPQ/ONDP/DNDP/Branch 2

Dated: 05/05/2020

Soumya Mitra

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Stephen Miller

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	NDA 213983 (crossreferenced to NDA 204790/SUPPL-25, TIVICAY® Tablets)
Assessment Cycle Number	Original-1
Drug Product Name/ Strength	Tablet for Oral Suspension (TOS); previously referred to as Dispersible Tablets (DT) / 5 mg
Route of Administration	Oral
Applicant Name	ViiV Healthcare
Therapeutic Classification/ OND Division	Antiviral/ DAV
RLD/RS Number	Not Applicable/505(b)(1) NDA
Proposed Indication	For treatment of HIV infection in patients aged ≥4 weeks and weighing at least 3 kg

Assessment Recommendation: *APPROVAL*

Assessment Summary:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Dissolution	Medium	Dolutegravir is a low solubility drug substance, per BCS criteria.	Acceptable	The proposed dissolution method and acceptance criterion* are adequate for routine QC testing of the proposed drug product.

*USP Apparatus II (paddle) at 50 rpm, 900 mL of 0.01M Phosphate buffer, pH 6.8; Q = (b)(4)% at 25 min

Additionally, the submitted in vitro and in vivo PK data/information are adequate to establish the bridge from the drug product used in the clinical/stability studies to the final proposed to-be-marketed drug product.

List Submissions being assessed:

Document(s) Assessed	Date Received
Original NDA (SDN-1)	12/12/2019
Response (Part 1) to Biopharmaceutics Information Request (SDN-4)	2/6/2020
Response (Part 2) to Biopharmaceutics Information Request (SDN-7)	2/25/2020
Response to Biopharmaceutics Information Request (SDN-11)	3/20/2020

Concise Description of Outstanding Issues:
None

B.1 BCS DESIGNATION

Per the Applicant and the Biopharmaceutics Review of NDA 204790 for the already marketed (TIVICAY®) conventional dolutegravir tablets, dolutegravir is a BCS-2 (low solubility, high permeability) drug substance.

Assessment:

Solubility: *Low*
Per the Applicant, the drug substance is slightly soluble in water (approximately 3.2 mg/mL at 25°C), and practically insoluble in aqueous buffer media with pH across the physiologic range (≥19.6 mcg/mL at 25 or 37°C?). The solubility of (b) (4) (the preferred API form) in various pH media after 48 hours is shown in Table 6 of 3.2.P.2.2.2 Formulation Development. The solubility of (b) (4) and (b) (4) drug substance after 4 hours in the proposed dissolution medium at 37°C is the same (0.039 mg/mL), but solubility kinetics data were not available. The pH-solubility data of the other API polymorphic forms are also not available.

Permeability: *High*
FDA's review of the NDA of TIVICAY® tablets states that dolutegravir is a high permeability drug substance (high passive membrane permeability (333 nm/s at pH 7.4). The proposed labeling of dolutegravir TOS states that the relative bioavailability of the tablets for oral suspension is approximately 1.6-fold higher than the TIVICAY® tablets.

Dissolution: *Moderate to Very Rapid ((b) (4) % within 15 min to 60 min, depending on medium pH)*
Dolutegravir Tablet for Oral Suspension (TOS, 5 mg) exhibits very rapid dissolution (b) (4) % in 15 min) in pH 4.5 and 6.8 buffer media, and almost rapid

dissolution in pH 1.2 medium (b) (4)% in 30 min; (b) (4)% in 60 min); refer to the comparative dissolution profile figure on page 13 of the Applicant's IR Response to Question 6 (SDN-4).

Dolutegravir TOS (previously referred to as Dolutegravir Dispersible Tablets) is an immediate release drug product intended to be dispersed in a small amount of water prior to be administered, or alternatively, ingested direct to mouth. Note that the proposed tablet for oral suspension is not scored, nor is intended to be split prior to dosing, so dissolution profile data of split tablet portions were not submitted nor required.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment:

DISSOLUTION METHOD – *Adequate*

With the exception of the presence of 0.05 mM EDTA, in the dissolution medium, the final proposed QC dissolution method parameters (as shown in Table 1) for Dolutegravir Tablets for Oral Suspension (TOS) 5 mg, are the same as those for the already approved dissolution method for the commercial TIVICAY® (conventional dolutegravir) tablets, 10 mg .

Table 1
Final Proposed Dissolution Method Parameters

Apparatus	USP <711> Apparatus II (paddle)
Dissolution medium volume	900 ± 9 mL
Dissolution medium	0.01M Phosphate buffer with 0.05 mM EDTA, pH 6.8
Dissolution medium temperature	37.0 ± 0.5°C
Rotation speed	50 rpm
Detection	HPLC or UV-Vis

Rationale for the Chosen Dissolution Method Parameters

(b) (4)

Discriminating Power and Stability Indicating Potential

The final proposed dissolution method for dolutegravir tablet for oral suspension was shown to be capable of detecting (1) differences in (b) (4) process parameters (i.e., (b) (4) , and (2) storage-dependent stability-indicating product quality changes; refer to Figure 3 and Figure 4 of the Dissolution Method Development Report/DMDR incorporated in Section 3.2.P.5.3 Validation of Analytical Procedures. The data in *Figure 3 of the DMDR support the proposed operating ranges for* (b) (4) *.* Greater deviations from the target manufacturing process parameter ranges, as well as from recommended storage conditions are anticipated to produce greater deviations from the dissolution profile of the target drug product. For example, in Figure 1 of Applicant's Response to Biopharmaceutics Information Request in SDN-4, the final proposed QC dissolution method was demonstrated to be capable of rejecting a tablet lot that was subjected to a longer (3 months) duration of intentional stress stability testing.The Applicant correlated such stress-induced decrease in dissolution to the observed increase in the tablet's (b) (4) (as shown in Table 1 of the Response), (b) (4) .

Particle Size (X_{90} = NMT (b) (4) um by volume, using Laser Diffraction) of (b) (4) API (synthesized by either Route (b) (4)), and XRPD testing for (b) (4) are part of the approved/established API QC Specifications for the commercial TIVICAY® 10 mg, 25 mg, 50 mg Tablets (and crossreferenced by this NDA for the Dolutegravir Tablet for Oral Suspension, 5 mg). Per the Applicant, (b) (4) does not impact the

polymorphic form of the API, and change from [redacted] to any of the other known polymorphic forms ([redacted]) does not occur during drug substance manufacture, drug product manufacture and storage. *Based on the reported X_{90} range ([redacted] um, [redacted] of [redacted] drug substance batches used in the manufacture of TOS clinical lots (from a dissolution control perspective), this Reviewer considers the Applicant's proposal to adopt the input API particle size specification approved for TIVICAY tablets (X_{90} = NMT [redacted] um) to be reasonable.*

[redacted] are considered by the Applicant as critical process parameters. Thus, [redacted].

For the overall evaluation and final determination of the adequacy of the proposed drug substance, in-process, and finished drug product QC specifications for dolutegravir TOS, refer to the respective CMC reviews.

Analytical Method Validation

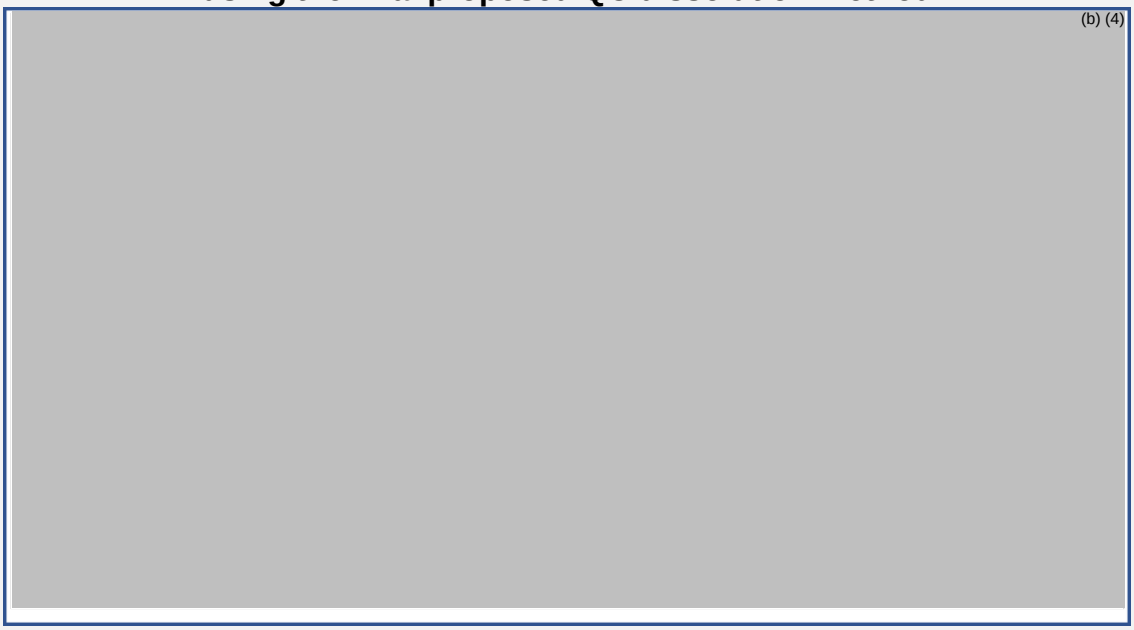
Quantification of drug in the dissolution samples is to be accomplished using UV or HPLC. Per the Applicant, HPLC by UV with Diode Array Detection with λ max of 258 nm (similar to the chromatographic conditions for Identity, Content, and Uniformity of Dosage Units) provides greater precision when performing dissolution manually. Both UV-Vis and HPLC/UV methods were evaluated for specificity, precision, linearity, robustness (with respect to chromatographic parameters), solution stability, and filter compatibility. Additionally, the dissolution method was investigated for robustness of the following parameters: medium pH (6.8 ± [redacted]), volume (900 ± [redacted] mL), buffer concentration (0.01 ± [redacted] M) & EDTA concentration (0.5 ± [redacted] mM), and paddle speed (50 ± [redacted] rpm), as well as equivalence of manual (HPLC) and automated (UV) methods. *Per the Drug Product Reviewer (Dr. Soumya Mitra), both HPLC/UV and UV-Vis methods are adequate for assay of dolutegravir in the dissolution samples.*

Sink Conditions
The solubility of dolutegravir sodium in 0.01M phosphate buffer pH 6.8 is 36.7 mg in 900 mL, thus sink conditions are expected to be achieved and maintained during routine QC dissolution testing of TOS 5 mg.

DISSOLUTION ACCEPTANCE CRITERIA – *Acceptable*

Based on the dissolution profile data of the pivotal clinical trial (P1903) lots, the proposed dissolution acceptance criterion, as well as (as explained above) based on the capability to reject intentionally stressed samples and other drug product lots manufactured with unacceptable quality attributes, "Q = (b) (4)% at 25 min" is acceptable. Refer to Figure 1 below for the dissolution profiles of the pivotal clinical lots (and primary stability lots) at the current long-term stability time point (using the proposed commercial dissolution method). Figure 1 on page 10 of the Applicant's Response (in SDN-4) shows that the profiles of the same drug product lots generated using the "clinical"/original/not-final dissolution method were comparable to those generated using the final/proposed commercial dissolution method.

Figure 1
Dissolution Profiles of Pivotal Phase 3 Clinical and Primary Stability Lots, using the final proposed QC dissolution method



Reviewer Note 1 (Legend): includes dissolution profiles of current long-term stability samples. The lots that appear with a yellow highlight in the figure were used in the pivotal Phase 3 clinical trial (P1093).
Reviewer Note 2 (age of clinical lots): *At the time of use in Study P1093, the clinical lots were ~11 to 35 months old. Based on the age information provided in SDN-7, this Reviewer*

presumes that at least some of the clinical lots included in the above figure are >36 months old at the time of in vitro dissolution testing.

Reviewer Note 3 (regarding "Safe space" for dissolution): *The proposed/recommended dissolution acceptance criterion is "Q = (b) (4)% at 25 min". Per the approved labeling of TIVICAY (25 mg) conventional tablets, dolutegravir 250 mg suspension did not prolong the QT interval. Additionally, there was no observed relationship between dolutegravir Cmax or AUC_{0-24} and adverse events/safety labs in the pediatric participants of Studies P1093 and ODYSSEY. The study report of Relative BA Study 205893 states that the dolutegravir (median)Tmax values for dolutegravir TOS 5 mg dispersed in water or taken direct to mouth, and TIVICAY 25 mg conventional tablets taken direct to mouth are 1 hr and 1.75 hr, respectively. Also, in addition to Tmax, the mode of TOS administration (as aqueous dispersion or as intact tablet) did not impact dolutegravir Cmax and AUC. Thus, the release for marketing of TOS tablets exhibiting faster in vitro dissolution (with or without prior dispersion in water) is not expected to pose a clinically significant safety concern.*

Dissolution on Stability

The Applicant reported no significant change in dissolution of the stability samples, with all results complying with the proposed specification.

Based on 24 months of long-term (30°C/75% RH) stability data and 6 months of accelerated (40°C/75% RH) stability data for three primary registration batches of the dolutegravir tablets for oral suspension (TOS, 5 mg), as well as based on simulated in-use stability data (30°C/75% RH for 60 days), the proposed expiration dating period for the TOS in the proposed commercial packaging is 36 months when stored below 30°C. The Applicant reported that the 6 months long-term and accelerated stability data for one supportive stability tablet batch (manufactured using API from synthesis (b) (4)) are consistent with those observed for the primary stability batches. *For the overall evaluation of the stability studies and proposed expiration dating period, refer to the Drug Product CMC review.*

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

Bridging of Phase 3 Clinical/Primary Stability Lots to Final Proposed To-Be-Marketed Dolutegravir Tablet for Oral Suspension (TOS):

The final proposed to-be-marketed/commercial formulation composition (Product Code CQ) and manufacturing process/site/scale were used to produce the final commercial image Dolutegravir Tablets for Oral Suspension (TOS, 5 mg) used in the (***i***) Pivotal pediatric Phase 3 Clinical Trial (IMPAACT P1093/ ING112578) and supportive PK substudies of ODYSSEY/Study 201296/PENTA 20, and (***ii***) Relative BA Study 205893/Part 2 (5 x 5 mg TOS vs. 1 x 25 mg TIVICAY conventional tablet) in healthy adults, as well as in (***iii***) primary stability studies.

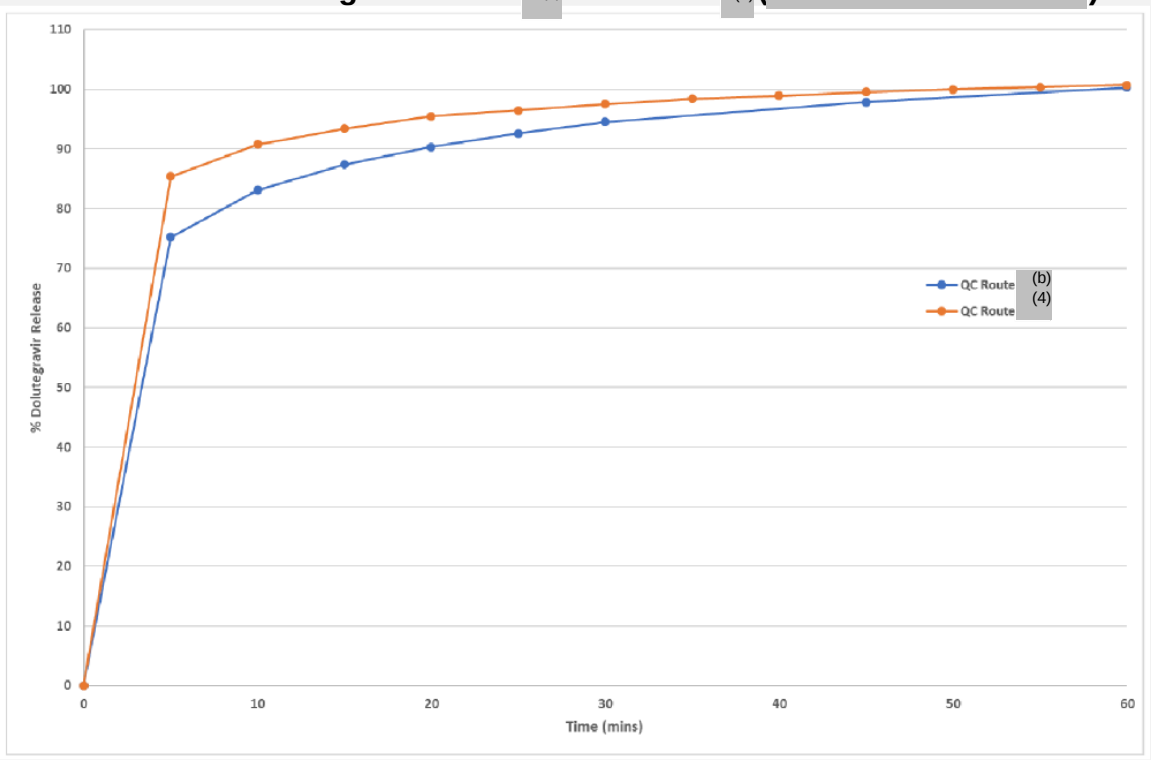
The TOS used in the clinical and stability studies were packaged in HDPE bottles (with 2 gram silica gel as desiccant) that (except for a different cap induction seal liner) are representative of the proposed commercial container-closure

configuration. For marketing, the bottle will be co-packaged with a dosing cup and oral dosing syringe (convenience kit) similar to the ones used in the clinical trials. The decision to increase the nominal volume capacities from (b) (4) mL to 30 mL (dosing cup) and (b) (4) mL to 10 mL (syringe) was based on the results of the Human Factors Study (in order to prevent spillage risk and allow for better swirling to facilitate dispersion of the drug product). Per the Applicant, the follow-up review and re-score suggest that no additional risks were introduced with the change in the size of the dosing cup (minimum volume measurable = 5 mL in place of (b) (4) mL). The recommended amounts of water for dispersing the tablets is the same as shown in the Instructions for Use (IFU) used in the HF Study and the IFU proposed for commercial use. Additionally, based on the instructions used in Study P1093, the resulting dolutegravir dispersion “concentrations” in the clinical trial are similar to what would be achieved when following the proposed commercial IFU (1 to 2.5 mg/mL versus 1 to 3 mg/mL), thereby ensuring similar oral palatability profiles of the clinical vs. commercial suspension drug products.

In the SDN-4 Response to the Biopharmaceutics information request, the Applicant confirmed that dolutegravir TOS manufactured using input API synthesized using (b) (4) but not (b) (4) (i.e., (b) (4) had so far been used in clinical trials. However, the very rapid dissolution profiles of the (b) (4) and (b) (4) drug products using the proposed QC dissolution method (as shown in Figure 2 below) support comparability of the API synthetic (b) (4) That the intact (b) (4) showed slightly faster dissolution than the intact (b) (4) in the proposed dissolution medium, as well as in various pH media (as shown in Figures 2 to 4 on pages 15 & 16 of SDN-4) does not pose a significant concern from a safety perspective for the following reasons: (1) In clinical trials, the (b) (4) was administered after dispersal in water, which results in an even more rapid and instantaneous dissolution (b) (4)) than the intact (b) (4). (2) The Applicant pointed out (and the Dr. Qin Sun, Clinical Pharmacology Reviewer confirmed) that in Relative BA Study 205893, the dolutegravir Cmax, Tmax, and AUC of the aqueous dispersion of (b) (4) were comparable to those reported following administration of an equal dosage of (b) (4) given direct to mouth (refer to Figure 6 on page 18 of the IR Response) despite (as anticipated) the relatively faster in vitro dissolution of dispersed versus intact (b) (4) tablets; note that the median dolutegravir Tmax was reported to be 1.0 hour, with and without prior dispersion of the TOS 5 mg. (3) Per the approved labeling of TIVICAY® (25 mg conventional) tablets and the proposed labeling of TOS 5 mg, dolutegravir does not prolong the QT interval, even after oral administration of dolutegravir 250 mg suspension. (4) Per the Clinical Pharmacology Review Team, exposure-safety relationships for adverse events and safety laboratory values were not observed in both Studies P1093 and ODYSSEY.

REVIEWER NOTE:
Proposed Dolutegravir Tablet for Oral Suspension (5 mg) vs. Approved TIVICAY® Conventional Tablet (10 mg, 25 mg, 50 mg):
In the Applicant's updated PopPK analysis (and as confirmed by the Clinical Pharmacology Reviewer), "Formulation" (i.e., conventional tablet versus tablet for suspension, granules) was determined to be a significant covariate of dolutegravir PK. Note also that the proposed labeling states (and Dr. Sun verified) that the TIVICAY conventional tablets and the TOS are not bioequivalent on a mg-per-mg basis, and thus not interchangeable because the relative BA of the TOS is approximately 60% higher.

Figure 2
Comparative Dissolution Profiles of Tablets for Oral Suspension manufactured using API Route (b) (4) and Route (b) (4) ((b) (4))



Reviewer Notes: The profile similarity (f_2) value was not calculated because both Batch 354E ((b) (4)) and Batch R846801 ((b) (4)) exhibited very rapid dissolution.
The clinical and process validation tablet lots were manufactured using API-(b) (4)(manufactured by by the current commercial manufacturer, (b) (4).) whereas the proposed commercial drug product will be manufactured using API-(b) (4) or API-(b) (4)(manufactured by GSK (b) (4)/(b) (4)).
Source: Figure 1 on page 14 of the Applicant's IR Response (SDN-4).

B. 13 BIOWAIVER REQUEST

Assessment: ***Not Applicable***

A biowaiver request for non-bio-strengths was not submitted nor is it required because only one strength (5 mg) of the TOS is proposed for marketing.

A request to waive the requirement to conduct in vivo BA/BE studies is also not applicable because Clinical PK/PD/Efficacy/Safety data are available for the proposed commercial drug product, and (as stated in Section B.12 above) there are adequate in vitro and in vivo PK information to support the comparability of the API-Route (b) (4) versus the proposed alternate API-Route (b) (4)

R. REGIONAL INFORMATION

Post-Approval Commitments

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date:
Gerlie Gieser, Ph.D. (4/23/2020)

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Elsbeth Chikhale, Ph.D. (4/24/2020)

Gerlie Gieser

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Elsbeth Chikhale

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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/

STEPHEN MILLER
05/19/2020 12:37:18 PM