CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219792Orig1s000

PRODUCT QUALITY REVIEW(S)

Title:	NDA IQA Template Title Page-EXEC SUMMARY
Document ID:	OPQ-ALL-TEM-0040
Effective Date:	26 Sep 2023 Revision: 00
Total Pages:	5

Template Revision: 03

Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	219792
Applicant Name	UCB, Inc.
Drug Product Name	KYGEVVI (doxecitine/doxribtimine)
Dosage Form	For Oral solution
Proposed Strength(s)	2 g/2 g
NDA Classification	Type 1 - NME
Route of Administration	Oral
Maximum Daily Dose	800 mg/kg/day (divided into 3 doses)
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of thymidine kinase 2 deficiency (TK2d) in adults and pediatric patients with an age of symptom onset on or before 12 years
Drug Product Description	UCB Inc. has submitted this 505(b)(2) new drug application for KYGEVVI (doxecitine/doxribtimine) for oral solution, 2 g/2 g indicated for the treatment of thymidine kinase 2 deficiency (TK2d) in adults and pediatric patients with an age of symptom onset on or before 12 years. To assist with preparation, dosing, and storage of KYGEVVI reconstituted oral solution for up to 16 hours since multiple daily dosing are needed, the pharmacist will dispense the ZX2000 administration kit when the prescription is filled. The administration kit is not co-packaged with the drug product. Each drug product packet contains 2 g of doxecitine and 2 g of doxribtimine as active ingredients, and (b) (4) mg of magnesium stearate ((b) (4)) and (b) (4) mg of (b) (4) as inactive ingredients.

	This drug product should be stored at 20°C to 25°C (68° to 77°F); excursion permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Based on the stability data provided in the application, an expiration dating period of 30 months has been granted for this drug product. In-use stability data provided in the application supports storage of the reconstituted solution for up to 16 hours at room temperature and/or under refrigeration.		
Co-packaged product information	N/A		
Device information	The ZX2000 administration kit consists of a mixing bottle with dosing cup (ZX1000 dosing system) and a 10-mL oral syringe. This kit will be used for preparation of the oral solution, dosing, and up to 16-hour storage of reconstituted oral solution intended for multiple daily administration. The ZX2000 administration kit is not co-packaged with the drug product and is dispensed directly to patients (or patients' caregivers) by the pharmacy.		
Storage Temperature/ Conditions	20°C to 25°C (68° to 77°F); excursion permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature] In-use stability data provided in the application supports storage of the reconstituted solution for up to 16 hours at room temperature and/or under refrigeration.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Zhixing Shan, PhD	Lawrence Perez, PhD
	Drug Product/ Labeling	Apipa Wanasathop, PhD	Hamid Shafiei, PhD/Julia Pinto, PhD
	Manufacturing	Hao, Li, PhD	Jingbo Xiao, PhD
	Biopharmaceutics	N/A	N/A

	Microbiology	N/A	N/A
	Categorical Exclusion	Apipa Wanasathop, PhD	Hamid Shafiei, PhD
	RBPM	Emma Gimose	
	ATL	Hamid Shafiei, PhD	
Consults			

2. Final Overall Recommendation - Approval

During the manufacturing of doxribtimine, a potential genotoxic impurity, alpha-hydroxythymidine, is formed. The applicant has committed to controlling this impurity at (b) (4) ppm, which represents the lowest achievable limit. However, based on the maximum daily dose of 28g of doxribtimine, the proposed control limit of (b) (4) ppm for alpha-hydroxythymidine exceeds the exposure limit of 1.5 µg/day for potential genotoxic impurities as recommended in ICH M7(R2).

Following a risk-benefit assessment conducted by the clinical review team, the proposed limit of (b) (4) ppm has been determined to be acceptable. The email from Dr. Yuliya Yasinskaya (MD), Deputy Director of the Division of Rare Disease and Medical Genetics, reflecting this risk-benefit analysis has been captured in both the Drug Substance and Drug Product chapters of the Integrated Quality Assessment (IQA).

Therefore, this application is recommended for approval from the OPQ perspective.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

- The applicant of this 505(b)(2) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substances, doxecitine and doxribtimine as well as the drug product, KYGEVVI (doxecitine/doxribtimine) for oral solution, 2 g/2 g.
- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC-recommended revisions/changes to the PI labeling as well as container and carton labels have been appropriately addressed.

- The applicant request for categorical exclusion from the preparation of environmental assessment has been found valid and therefore, the categorical exclusion is granted.

Therefore, this application is recommended for approval from the OPQ perspective with an expiration dating period of 30 months.

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

Recommendation by Subdiscipline:

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

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): Yes

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

Application Technical Lead Name and Date:

Hamid Shafiei, Ph.D.
Senior Pharmaceutical Quality Assessor
DPQA VII/OPQA II/OPQ

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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 (OPQ-ALL-WI-0006)

NDA Number	219792
Assessment Cycle Number	1
Drug Product Name	KYGEVVI (doxecitine/doxribtimine) for oral solution, 2 g/2 g

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	eCTD #0025, SDN# 25 eCTD #0030, SDN# 30 eCTD #0034, SDN# 34 eCTD #0039, SDN# 39
Patient Information	Adequate	eCTD #0001, SDN# 1
Instruction for Use (IFU)	Adequate	eCTD #0001, SDN# 1 eCTD #0039, SDN# 39
Container Labels	Adequate	eCTD #0001, SDN# 1 eCTD #0039, SDN# 39
Carton Labeling	Adequate	eCTD #0001, SDN# 1 eCTD #0039, SDN# 39

Brief Description of Outstanding Issues:

All the provided labeling document contains adequate information with minor revisions listed below.
All the recommendations have been communicated to the applicant through clinical team and accepted prior to approval.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
eCTD #0001, SDN# 1	12/16/2024	All labeling information
eCTD #0025, SDN# 25	04/22/2025	Prescribing Information revision
eCTD #0030, SDN# 30	05/30/2025	Prescribing Information revision
eCTD #0034, SDN# 34	07/15/2025	Prescribing Information, IFU, and PPI revision
eCTD #0039, SDN# 39	09/04/2025	Prescribing Information, IFU, and carton revision

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(copy of proposed text)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KYGEVVI safely and effectively. See full prescribing information for KYGEVVI.

KYGEVVI (doxecitine and doxribtimine) powder, for oral solution

Initial U.S. Approval: YYYY

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

Powder for oral solution: 2 g doxecitine and 2 g doxribtimine. (3)

Item	Item 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[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	
Route(s) of administration	Adequate	
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Inadequate	Pending approval year
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	

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

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

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

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

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

Item	Item 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)
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	N/A	Not a salt
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.[8]	N/A	

Assessment: *Adequate*

The highlights contained all the required information in the correct format. The only pending information is the initial U.S. approval year.

[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(*copy of proposed text*)

2.4 Preparation and Administration Instructions
Use Table 2 for preparation and administration information.
Use the ZX2000 administration kit provided separately to prepare and administer the prescribed dose [see HOW SUPPLIED/STORAGE AND HANDLING (16)]. Refer to the Instructions for Use for full preparation and administration information on use of KYGEVVI with the ZX2000 administration kit. Household devices such as measuring cups or spoons are not adequate measuring devices.

Preparation Instructions
Preparation of KYGEVVI with a liquid other than water has not been studied clinically and is not recommended. (b) (4)
1. Obtain the required number of KYGEVVI packets to prepare a one-day supply of solution each morning.
2. Use 40 mL of water per packet. Pour the prescribed volume of room temperature water (between 20ºC - 25ºC or 68ºF - 77ºF) into the mixing bottle.
3. Add the powder from the required number of KYGEVVI packets into the mixing bottle.
4. Screw the dosing cup tightly onto the mixing bottle and (b) (4) at least 20 times. (b) (4) repeat until the powder dissolves.
5. The mixed solution may appear cloudy and have some residual (b) (4) (inactive ingredients) remaining at the bottom or top.

Administration Instructions
(b) (4)
Oral Administration
1. Before each administration, (b) (4) at least 3 times.
2. Use 1 of 2 methods (dosing cup or oral syringe) to administer KYGEVVI oral solution. Choose the method based on the volume of solution to be administered per dose.
3. (b) (4) KYGEVVI (b) (4) solution in 3 equally divided doses approximately 6 hours apart (± 2 hours) with food.
4. Do not administer another dose if the dose is spit out or if a complete dose is not taken. Take the next dose at the next scheduled time.
5. Discard any remaining KYGEVVI solution (b) (4)

Feeding Tube Administration

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

KYGEVVI [redacted] (b) (4) is compatible with the most commonly available feeding tubes. To flush the tube, a single flushing step with a volume of water equivalent to the tube's priming volume is sufficient.
Follow the instructions of the feeding tube to administer [redacted] (b) (4).
Discard any remaining KYGEVVI solution [redacted] (b) (4).

2.5 Storage Instructions for Prepared KYGEVVI Solution
• Store [redacted] (b) (4) KYGEVVI solution at controlled room temperature at 20°C to 25°C (68°F to 77°F) or refrigerate between 2°C to 8°C (36°F to 46°F).
• Discard KYGEVVI [redacted] (b) (4) solution 16 hours after reconstitution.

Item	Item 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 and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	Adequate	
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 should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling	N/A	No USP monograph for this product

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments
[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition

Item	Item 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)
requirement may be applicable to another section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: *Adequate*

The recommendations on administration kit and storage condition have been communicated to the applicant and accepted in eCTD #0030, SDN# 30.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

(*copy of proposed text*)

Powder for oral solution: 2 g doxecitine and 2 g doxribtimine as white to off-white powder in a single use packet.

Item	Item 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	N/A	

[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item 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)
ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.		
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 parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Assessment: *Adequate*

This section contained all the required information in the correct format.

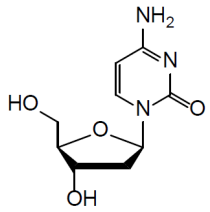
1.2.3 Section 11 (DESCRIPTION)[14]

(*copy of proposed text*)

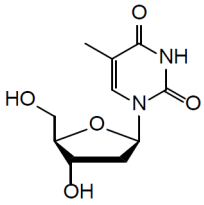
KYGEVVI is a combination of doxecitine and doxribtimine, both of which are pyrimidine nucleosides. KYGEVVI is a powder for oral solution. Both doxecitine and doxribtimine are white to off-white powders and soluble in water.

Doxecitine
The chemical name of doxecitine is 4-Amino-1-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one. The molecular formula is $C_9H_{13}N_3O_4$ and the molecular weight is 227.22. The chemical structure is:

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)



Doxribtimine
The chemical name of doxribtimine is 1-((2R,4S,5R)-4-Hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione. The empirical formula is $C_{10}H_{14}N_2O_5$ and the molecular weight is 242.23. The chemical structure is:



Each packet of KYGEVVI powder contains 2 grams doxecitine and 2 grams doxribtimine. The inactive ingredients are colloidal silicon dioxide and magnesium stearate.

Item	Item 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)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	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)" [§ 201.57(c)(12)(i)(C)].	N/A	

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

Item	Item 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)
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	Changed the (b) (4) to its USP/NF name.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	Pharm/Tox confirmed the EPC class.
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	

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

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

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

Item	Item 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)
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	It was mentioned that both chemicals are soluble in water.
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	Not proposed by the applicant
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Assessment: *Adequate*

The excipient name has been changed to USP/NF name and the Pharmacological class has been added according to Pharm/Tox recommendation. Pharm/Tox has provided the EPC class through email communication on 4/3/2025.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(*copy of proposed text*)

How Supplied
KYGEVVI is supplied as follows:
Package 1 of 2:
NDC 50474-350-01: Each single use packet contains 4 g of KYGEVVI as a white to off-white powder (2 g doxecitine and 2 g doxribtimine)
NDC 50474-350-30: Carton contains 30 packets

Package 2 of 2
The ZX2000 administration kit for use with KYGEVVI is supplied separately and contains the following:

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)
[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

• One dosing system (includes mixing bottle and dosing cup)
• Two 10 mL oral syringes
• Two spare seals

Storage and Handling
Store KYGEVVI packets at 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Store KYGEVVI solution (b) (4) at controlled room temperature or refrigerated. Discard KYGEVVI solution 16 hours after reconstitution *[see Dosage and Administration (2.5)].*

Item	Item 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) [§ 201.57(c)(17)].	Adequate	
Strength(s) in metric system. [§ 201.57(c)(17)(i)] 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. No equivalency statement.	Adequate	
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	
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 parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Item	Item 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)
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." [§ 201.57(c)(17)(iv)]	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	Revised to USP recommendation
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."*[21]	N/A	
Include information about child-resistant packaging[22] (if chosen by manufacturer).	N/A	

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)

Assessment: *Adequate*

The recommendations have been communicated to the applicant and accepted in eCTD #0030, SDN# 30.

- The information about the administration kit as recommended by the PQL email communication on 4/29/2025 below:

  Recommendation

  We agree with OSE/DMEPA to include information regarding the administration kit in the PI in both section 2 DOSAGE AND ADMINISTRATION and section 16 HOW SUPPLIED STORAGE AND HANDLING to help minimize dosing errors. Additionally, it is unclear how end-users will obtain the required administration kit. The Applicant should provide this information in the submission to better understand how end users will interact with the DP and administration kit.

  Rationale

  The regulations are not explicit on whether to include or not include information related to administration kits (or ancillary materials) that are supplied separately and not co-packaged with the drug product. We recognize there have been varying labeling approaches for drug products that are either co-packaged with ancillary materials or supplied separately. However, OSE/DMEPA noted some Human Factors (HF) study participants did not identify or notice the administration kit and chose to use their own measuring cup/container, which may lead to dosing errors.

  For DPs subject to PLR format:

  • *Section 2 Dosage and Administration "must also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams of active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed (e.g., the rate of administration of parenteral drug in milligrams per minute;…" per 21 CFR 201.57(c)(3)(iv).*

  >> In this scenario, the preparation instructions should include information about the administration kit

  • *Section 16 How Supplied/Storage and Handling must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible per 21 CFR 201.57(c)(17)(iv). In addition to the strength, dosage form, and packaging information, it is likely that a HCP will look in this section to determine if the administration kit is included in the packaged DP.*

  >> It is helpful for an HCP to know that a required administration kit in not included in the supplied packaging.

  Additionally, it is unclear how end-users will obtain the required administration kit. The Applicant should provide this information in the submission to better understand how end users will interact with the DP and administration kit.

1.2.5 Other Sections of Labeling

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

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

None

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

KYGEVVI manufactured for:
UCB, Inc.
Smyrna, GA 30080

KYGEVVI® is a trademark of the UCB Group of Companies.
©XXXX, UCB, Inc., Smyrna, GA 30080
All rights reserved.

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	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	

Assessment: *Adequate*

[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

2.0 PATIENT LABELING

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

INSTRUCTIONS FOR USE

Storing KYGEVVI packets and oral solution:

• KYGEVVI (b) (4) solution should be prepared on the same day as taking or giving your daily dose.

• Store KYGEVVI packets (b) (4) at room temperature between 20°C – 25°C (68°F -77°F).

• Store (b) (4) solution at room temperature between 68°F to 77°F (20°C to 25°C) or in the refrigerator between 36°F to 46°F (2 to 8°C).

• Make sure (b) (4) when storing your KYGEVVI oral solution to avoid spills or leaks.

• When storing or carrying the (b) (4), keep the mixing bottle upright.

• (b) (4). Discard any oral solution remaining after 16 hours or after the 3 doses have been administered, whichever is sooner.

• Keep KYGEVVI and all medicines out of reach of children.

PATIENT INFORMATION

KYGEVVI comes as a (b) (4).

o (b) (4) you are ready to use them.

• (b) (4) room temperature (b) (4) water. Do not mix with any other liquids or foods.

o (b) (4) use the mixing bottle and dosing cup provided (b) (4). Do not use a household measuring cup or measuring spoons.

o See the detailed “Instructions for Use” that comes with KYGEVVI for important information about the correct way to (b) (4) and take a dose of KYGEVVI (b) (4) solution.

How should I store KYGEVVI?

• Store KYGEVVI packets at controlled room temperature between 20°C – 25°C (68°F - 77°F).

• Store the prepared (b) (4) solution at room temperature between 68°F to 77°F (20°C to 25°C) or refrigerate between 36°F to 46°F (2°C to 8°C).

• KYGEVVI (b) (4) solution (b) (4) within 16 hours following preparation. Discard any (b) (4) solution remaining after 16 hours or after the 3 doses have been administered, whichever (b) (4).

Keep KYGEVVI and all medicines out of the reach of children.

What are the ingredients in KYGEVVI?

Active ingredients: doxecitine and doxribtimine.

Inactive ingredients: colloidal silicon dioxide and magnesium stearate.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[24]	Adequate	
Special preparation instructions (if applicable).	Adequate	
Storage and handling information (if applicable).	Adequate	Revised the storage condition to comply with USP Controlled Room Temperature
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.	N/A	
Active ingredient(s) (if applicable).	Adequate	
Alphabetical listing of inactive ingredients (if applicable).	Adequate	Changed the (b) (4) to its USP/NF name.
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Adequate*

The recommendations have been communicated to the applicant and accepted in eCTD #0034, SDN# 34.

- Revise the storage condition to comply with USP Controlled Room Temperature.
- Change the silica colloidal anhydrous to its USP/NF name.

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

3.0 CONTAINER AND CARTON LABELING[25]

3.1 Container Labels[26]

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

3.2 Carton Labeling

(Copy/paste or refer to a representative example of a proposed carton labeling)

[25] Carton and Container Labeling Resources

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

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	N/A	Yes	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Yes	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	No	Different NDC is listed on the packet and the carton
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	Revision made in eCTD#39

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

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

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

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

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

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	N/A	No	Listed on the carton, not on the container
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Yes	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Yes	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Yes	
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.[31]	N/A	Yes	
And others if space is available.	N/A	Yes	

[31] USP General Notices 3.20 Indicating Conformance

Assessment of Carton Labels and Container Labeling: *Adequate*
The recommendations have been communicated to the applicant and accepted in eCTD #0039, SDN# 39.

- Revising the word (b) (4) to “packet”
- Since this product is not co-packaged with the administration device, it should be stated on the carton. Add the device information on the carton labeling to ensure that it is used with the correct device.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

The labeling is adequate. All the recommendations have been communicated to the applicant through clinical team and accepted prior to approval.

- In the *Highlights* section, pending information is the initial U.S. approval year.

Primary Labeling Assessor Name and Date: Apipa Wanasathop (09/17/2025)

Secondary Assessor Name and Date (and Secondary Summary, as needed): Julia Pinto (09/17/2025)

Apipa Wanasathop

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Julia Pinto

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Date: 9/17/2025 03:07:08PM
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