CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217865Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality

New Drug Application (NDA) 217865
Integrated Quality Review – Addendum 2

This addendum to the Integrated Quality Review for NDA 217865 dated 9/26/2023 and Addendum 1 (10/26/2023) conveys the OPQ recommendation for APPROVAL of the NDA. The revised recommendation is based on the applicant's commitment to conduct additional leachables studies under a post-marketing commitment (PMC).

NDA Executive Summary – Addendum 2

This addendum to the Executive Summary for NDA 217865 dated 9/26/2023 and Addendum 1 (10/26/2023) is based on the applicant's post-marketing commitment (PMC) with respect to leachable studies.

1. Application/Product Information

NDA Number	217865		
Applicant Name	Italfarmaco S.p.A.		
Drug Product Name	Duvyzat (Givinostat)		
Dosage Form	Suspension		
Proposed Strength(s)	8.86 mg/mL		
NDA Classification	Type 1 - NME		
Route of Administration	Oral		
Maximum Daily Dose	(b) (4) mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of Duchenne muscular dystrophy (DMD)		
Drug Product Description	White to off-white or faintly pink suspension		
Co-packaged product information	Each bottle is packaged with (b) (4) (b) (4), one 5 mL graduated oral syringe, and a bottle adapter.		
Device information	N/A		
Storage Temperature/ Conditions	20°C to 25°C. Do Not Freeze.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Zhixing Shan	Donna Christner
	Drug Product/ Labeling	Mariappan Chelliah	Martha Heimann
	Manufacturing	Miral Patel	Shu-Wei Yang

	Biopharmaceutics	Hansong Chen	Ta-Chen Wu
	Microbiology	Helen Ngai	Elizabeth Bearr
	Other (specify)	N/A	N/A
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation - Approval with QPA(s)

2. Action Letter Information

3.

a. Expiration Dating:

24 Months for product stored at 20°C to 25°C.

b. Additional Comments for Action

The following PMCs will be communicated in the Approval letter:

- Perform experimental activities to evaluate if the drug product matrix can be suppressed (e.g., drug product dilutions or interfering matrix precipitation/liquid extraction with recovery evaluation).
  Final reports submission: July 2024

- If matrix interference can be suppressed: Test the three drug product submission batches at their 36 months stability endpoint at 25°C/60% RH.
  Final protocol submission: July 2024
  Final report submission: December 2024

  In addition, to assess any trending, test the first three post-approval batches at multiple time points - from release through the end of proposed shelf-life.
  Results - submitted in the NDA annual reports.

- If matrix interference cannot be suppressed: Update regarding the on-going leachable study with simulant solvent and provide an overall risk assessment to evaluate if there is any significant risk associated to presence of leachables in our drug product.
  Interim reports with 24 months data submission: December 2024
  Final reports with 36 months data submission: December 2025

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The Office of Pharmaceutical Quality (OPQ) recommends **APPROVAL with QPAs** for NDA 217865, Duvyzat (givinostat) oral suspension 8.86 mg/mL. Except for extractables and leachables, the applicant has provided adequate information to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all facilities associated with this application. The proposed labeling and labels have adequate information to meet the regulatory requirements.

Extractables/Leachables QPA/PMC – The applicant conducted an adequate extractable study for the primary container closure system. The leachable study was deemed inadequate as the applicant conducted a simulated leachable study using 12% v/v ethanol in pH 5.0 water in lieu of a leachable study using the drug product. The rationale provided for the simulated leachable study was that the product matrix interfered with the analytical methods; however, the applicant had not demonstrated that the matrix interference could not be suppressed by modification of the analytical procedures, e.g., use of alternate columns, solvents or detection methods. While the simulated leachable study is not considered adequate. The currently available data are acceptable on an interim basis given the relatively low risk for leachables with a primarily aqueous and benefit for DMD patients' unmet medical needs. Thus, it is recommended that the applicant be allowed to address the leachables deficiency under a PMC.

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

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate with QPAs**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations
Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

Other than the PMCs discussed above, there are no outstanding issues or lifecycle considerations.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.

3/5/2024

Martha Heimann

Digitally signed by Martha Heimann
Date: 3/05/2024 04:37:43PM
GUID: 504f845f00000ed260627d268a8cdc9d

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Important: Do Not Change the Header or Footer

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	217865
Assessment Cycle Number	1
Drug Product Name	Givinostat

Assessment Recommendation: Choose an item.

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	SDN48
Patient Information	N/A	N/A
Instruction for Use (IFU)	N/A	N/A
Container Labels	Adequate	SDN 0055
Carton Labeling	Adequate	SDN 0055

Brief Description of Outstanding Issues: None

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
SDN 0048	01/24/2028	Prescribing Information
SDN 0055	02/28/2024	Carton/container labeling

1.0 PRESCRIBING INFORMATION[1]

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

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

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)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	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 ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	

[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>
[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)

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)
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*

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

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	

[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>

[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)

[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

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)
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Choose an item.	
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 requirement may be applicable to another section of the PI (e.g., Section 11).	Choose an item.	
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*

[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition

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

(*copy of proposed text*)

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 ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	Adequate	
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*

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

1.2.3 Section 11 (DESCRIPTION)[14]

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)].	Adequate	
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	
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	N/A	

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

[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).

[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.

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)
statement of effect. [§ 201.100(b)(5)(iii)].		
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	
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)].	Adequate	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	
For oral prescription drug products, include gluten statement[19] (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	N/A	

[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).

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

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)
to another section of the PI (e.g., Section 2).		

Assessment: *Adequate*

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

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	

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

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)
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	
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	
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]	Choose an item.	

[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)

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)
Include information about child-resistant packaging[22] (if chosen by manufacturer).	Adequate	

Assessment: *Adequate*

1.2.5 Other Sections of Labeling

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

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

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

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*

[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)
[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):

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).	N/A	
Storage and handling information (if applicable).	Adequate	
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	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Adequate*

3.0 CONTAINER AND CARTON LABELING[25]

[24] Established name = [Drug] [Route of Administration] [Dosage Form]
[25] Carton and Container Labeling Resources

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

3.2 Carton Labeling

(b) (4)

[redacted]

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	

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

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)
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)].	N/A	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>].	Choose an item.	Choose an item.	
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	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms	N/A	Yes	

[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)
include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).			
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	N/A	Yes	
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	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx,	N/A	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)
required for OTC [§ 201.66(c)(5)(x)].			
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	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	No	
And others if space is available.	N/A	Yes	

Assessment of Carton Labels and Container Labeling: *Adequate*

[31] USP General Notices 3.20 Indicating Conformance

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

None

Primary Labeling Assessor: Mariappan V Chelliah

Secondary Assessor: Martha Heimann

Mariappan Chelliah

Digitally signed by Mariappan Chelliah
Date: 3/05/2024 12:03:32PM
GUID: 5399cb2c00032b7c21877aa0d4d5f794

Martha Heimann

Digitally signed by Martha Heimann
Date: 3/05/2024 12:25:09PM
GUID: 504f845f00000ed260627d268a8cdc9d

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/

MARTHA R HEIMANN
03/05/2024 05:45:00 PM

Office of Pharmaceutical Quality

New Drug Application (NDA) 217865
Integrated Quality Review – Addendum

This addendum to the Executive Summary for NDA 217865 dated 9/26/2023 is based on additional consultation within ONDP regarding adequacy of the applicant's risk assessment for potential (b) (4) impurities. The applicant's risk assessment for (b) (4) is acceptable. However, the application remains deficient with respect to leachable studies.

NDA Executive Summary - Addendum

This addendum to the Executive Summary for NDA 217865 dated 9/26/2023 is based on additional consultation within ONDP regarding adequacy of the applicant's risk assessment for potential (b) (4) impurities. The applicant's risk assessment for (b) (4) is acceptable. However, the application remains deficient with respect to leachable studies.

1. Application/Product Information

NDA Number	217865		
Applicant Name	Italfarmaco S.p.A.		
Drug Product Name	Duvyzat (Givinostat)		
Dosage Form	Suspension		
Proposed Strength(s)	8.86 mg/mL		
NDA Classification	Type 1 - NME		
Route of Administration	Oral		
Maximum Daily Dose	(b) (4) mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of Duchenne muscular dystrophy (DMD)		
Drug Product Description	White to off-white or faintly pink suspension		
Co-packaged product information	Each bottle is packaged with (b) (4) (b) (4) one 5 mL graduated oral syringe, and a bottle adapter.		
Device information	N/A		
Storage Temperature/ Conditions	20°C to 25°C. Do Not Freeze.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Zhixing Shan	Donna Christner
	Drug Product/ Labeling	Mariappan Chelliah	Martha Heimann

	Manufacturing	Miral Patel	Shu-Wei Yang
	Biopharmaceutics	Hansong Chen	Ta-Chen Wu
	Microbiology	Helen Ngai	Elizabeth Bearr
	Other (specify)	N/A	N/A
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation - Complete Response (CR)

3. Deficiencies

CR Deficiency:

1) *Extractable and Leachable Study:* Please refer to the extractable & leachable study submitted in the original submission and your response to information request submitted in SN0026. You have conducted a leachable study using a simulating solvent and justified this approach due to the interference of the drug product formulation itself. However, you have not demonstrated that the matrix interference could not be suppressed in any way. Therefore, your simulated leachable study is not acceptable. You should conduct sufficient investigation to mitigate the matrix interference.

Non-CR Deficiency:

Please refer to the drug product specification submitted in the original submission. The two specified impurities (b) (4) are controlled at NMT (b) (4)% and NMT (b) (4)% respectively. However, you are reporting them as a percentage of "givinostat hydrochloride monohydrate". Because the drug product strength in the labelling will be in terms of "givinostat", you should report these impurities as a percentage of "givinostat". In addition, for the calculation, you should use the molecular weights corresponding to the (b) (4)

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The Office of Pharmaceutical Quality (OPQ) recommends a **COMPLETE RESPONSE** for NDA 217865, Duvyzat (givinostat) oral suspension 8.86 mg/mL. The applicant has not provided adequate information to ensure the identity, strength,

purity, and strength of the proposed drug product. The outstanding issue is related to control of leachables/extractables in the product which are discussed below.

Extractables/Leachables – The Applicant conducted an adequate extractable study for the primary container closure system, but the leachable study is deemed inadequate. The Applicant stated that, because of matrix interference, they chose to conduct a simulated leachable study using 12% v/v ethanol in pH 5.0 water in lieu of a leachable study using the drug product. The applicant has not demonstrated that the matrix interference could not be suppressed by modification of the analytical procedures, e.g., use of alternate columns, solvents or detection methods. Because the Applicant did not conduct adequate studies to mitigate the matrix interference, the data from a simulated study is not acceptable to the Agency. Given the relative lower risk for leachables with a primarily aqueous oral solution and a potential benefit for DMD patients, a post-marketing commitment for an adequate leachable study could be appropriate. However, the clinical division has indicated that clinical deficiencies preclude approval of the NDA in its current form. Therefore, this will be communicated as a CR deficiency.

The overall manufacturing inspection recommendation is approval for all facilities associated with this application. Review of labeling is deferred.

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

Recommendation by Subdiscipline:

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

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

Not applicable as the application is not recommended for approval.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.

10/26/2023

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

MARTHA R HEIMANN
10/26/2023 03:50:53 PM

NDA Executive Summary

1. Application/Product Information

NDA Number	217865		
Applicant Name	Italfarmaco S.p.A.		
Drug Product Name	Duvyzat (Givinostat)		
Dosage Form	Suspension		
Proposed Strength(s)	8.86 mg/mL		
NDA Classification	Type 1 - NME		
Route of Administration	Oral		
Maximum Daily Dose	(b) (4) mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of Duchenne muscular dystrophy (DMD)		
Drug Product Description	White to off-white or faintly pink suspension		
Co-packaged product information	Each bottle is packaged with (b) (4) (b) (4) one 5 mL graduated oral syringe, and a bottle adapter.		
Device information	N/A		
Storage Temperature/ Conditions	20°C to 25°C. Do Not Freeze.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Zhixing Shan	Donna Christner
	Drug Product/ Labeling	Mariappan Chelliah	Martha Heimann
	Manufacturing	Miral Patel	Shu-Wei Yang
	Biopharmaceutics	Hansong Chen	Ta-Chen Wu
	Microbiology	Helen Ngai	Elizabeth Bearr

	Other (specify)	N/A	N/A
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation - Complete Response (CR)

3. Deficiencies

CR Deficiencies:

1) *Extractable and Leachable Study:* Please refer to the extractable & leachable study submitted in the original submission and your response to information request submitted in SN0026. You have conducted a leachable study using a simulating solvent and justified this approach due to the interference of the drug product formulation itself. However, you have not demonstrated that the matrix interference could not be suppressed in any way. Therefore, your simulated leachable study is not acceptable. You should conduct sufficient investigation to mitigate the matrix interference.

2) (b) (4) *Risk Assessment:* Please refer to the risk assessment for (b) (4) submitted in the original submission and your response to information request submitted in SN0026. (b) (4) (b) (4)

Non-CR Deficiency:

Please refer to the drug product specification submitted in the original submission. The two specified impurities (b) (4) are controlled at NMT (b) (4)% and NMT (b) (4)% respectively. However, you are reporting them as a percentage of "givinostat hydrochloride monohydrate". Because the drug product strength in the labelling will be in terms of "givinostat", you should report these impurities as a percentage of "givinostat". In addition, for the calculation, you should use the molecular weights corresponding to the (b) (4).

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The Office of Pharmaceutical Quality (OPQ) recommends a **COMPLETE RESPONSE** for NDA 217865, Duvyzat (givinostat) oral suspension 8.86 mg/mL. The applicant has not provided adequate information to ensure the identity, strength, purity, and strength of the proposed drug product. There are two outstanding issues related to control of potential (b) (4) impurities and leachables/extractables in the product which are discussed below.

(b) (4) – The Applicant's risk assessment for potential (b) (4) impurities is not acceptable. The product formulation can potentially contain low levels of (b) (4) originating from an inactive ingredient, (b) (4). Because givinostat contains a (b) (4) the (b) (4) can potentially cause formation of (b) (4) Additionally, two specified impurities in the bulk drug substance, (b) (4) and (b) (4) contain the same (b) (4) and could potentially form (b) (4) in the product. Therefore, the Applicant should provide data to demonstrate the absence of (b) (4) impurities in the drug product or implement adequate control in the drug product specification.

Extractables/Leachables – The Applicant conducted an adequate extractable study for the primary container closure system, but the leachable study is deemed inadequate. The Applicant stated that, because of matrix interference, they chose to conduct a simulated leachable study using 12% v/v ethanol in pH 5.0 water in lieu of a leachable study using the drug product. The applicant has not demonstrated that the matrix interference could not be suppressed by modification of the analytical procedures, e.g., use of alternate columns, solvents or detection methods. Because the Applicant did not conduct adequate studies to mitigate the matrix interference, the data from a simulated study is not acceptable to the Agency. Given the relative lower risk for leachables with a primarily aqueous oral solution and a potential benefit for DMD patients, a post-marketing commitment for an adequate leachable study could be appropriate. However, the clinical division has indicated that clinical deficiencies preclude approval of the NDA in its current form. Therefore, this will be communicated as a CR deficiency.

The overall manufacturing inspection recommendation is approval for all facilities associated with this application. Review of labeling is deferred to a later review cycle.

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

Recommendation by Subdiscipline:

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

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

Not applicable as the application is not recommended for approval.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.

9/26/2023

64 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Because clinical is expected to provide a Complete Response to this application, the labeling is not being reviewed in this cycle. It will be reviewed when the Applicant resubmits this application.

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		
Established name(s)		
Route(s) of administration		
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally 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.		

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)		

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)		
Strength(s) in metric system		
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		
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.		

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)		
Dosage form(s) and route(s) of administration		
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.		
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.		
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.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		
Statement of being sterile (if applicable)		
Pharmacological/ therapeutic class		
Chemical name, structural formula, molecular weight		
If radioactive, statement of important nuclear characteristics.		
Other important chemical or physical properties (such as pKa or pH)		

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable		
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"		

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)		
Strength(s) in metric system		
Available units (e.g., bottles of 100 tablets)		
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally 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.		

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.)		
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."		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.		
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."		
Include information about child-resistant packaging		

1.2.5 Other Sections of Labeling

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

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

1.2.6 Manufacturing Information After Section 17 (for drug products)

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		

2.0 PATIENT LABELING

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

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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

3.2 Carton Labeling

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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence		
Dosage strength		
Route of administration		
If the active ingredient is a salt, include the equivalency statement per FDA Guidance		
Net contents (e.g. tablet count)		
"Rx only" displayed on the principal display		
NDC number		
Lot number and expiration date		
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.		
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 which require "Not for direct infusion" statement.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		
Bar code		

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor		
Medication Guide (if applicable)		
No text on Ferrule and Cap overseal		
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.		
And others, if space is available		

Assessment of Carton and Container Labeling: *{Adequate/Inadequate}*

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

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

Primary Labeling Assessor: Mariappan V Chelliah

Secondary Assessor: Martha R Heimann

Mariappan Chelliah

Digitally signed by Mariappan Chelliah
Date: 9/25/2023 03:11:09PM
GUID: 5399cb2c00032b7c21877aa0d4d5f794

Martha Heimann

Digitally signed by Martha Heimann
Date: 9/25/2023 03:14:39PM
GUID: 504f845f00000ed260627d268a8cdc9d

49 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

NDA 217865
Assessment # 01

CHAPTER VII: MICROBIOLOGY

For more details about the items in this template, please see Chapter VII (Microbiology) of the ANDA IQA Guide

Product Information	505(b)(1)
NDA Number	217865
Assessment Cycle Number	01
Drug Product Name / Strength	Established name: Givinostat. Proprietary name: Duvyzat oral suspension Strength: 8.86 mg/mL
Route of Administration	Oral
Applicant Name	Italfarmaco S.p.A.
Manufacturing Site	Italfarmaco S.p.A., Calle San Rafael 3, Poligono Industrial Alcobendas, Alcobendas, Madrid, Spain.
Method of Sterilization	None. Non-sterile suspension.

Assessment Recommendation: **Adequate**

Theme:

☒ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: *(Click link to view Justification Statements)*

N/A
Other (Requires Division Director Approval) – Assessor writes justification here if "other" selected as theme.

Assessment Summary: The submission **is recommended** for approval on the basis of product quality microbiology.

List Submissions Being Assessed:

Document(s) Assessed	Date Received
Orig-1 (SD 3)	4/21/2023
Orig-1 (SD 16)	7/20/2023

Highlight Key Issues from Last Cycle and Their Resolution:

Remarks: The application is granted priority review status. The internal goal dates are CMC mid cycle meeting 8/3/2023, CMC wrap up meeting 8/28/2023, QDD 9/7/2023, ODD 9/21/2023, PDUFA action 12/21/2023. The drug product manufacturing facility does not have FDA inspection history. A prior approval inspection is scheduled from 9/11/2023-9/15/2023.

Concise Description of Outstanding Issues: none

Supporting Documents:

Note to reviewer: Per the cover letter, CMC information was submitted as part of IND 126598. The IND was not reviewed by DMA.

Select Number of Approved Comparability Protocols: 0

S Drug substance – non sterile. N/A.

P Drug Product

P.1 Description of the composition of the drug product

(4/21/2023, 3.2.P.1., *desc-compo-drug-prod.pdf*)

- Description of drug product – The drug product is a white to off white or faintly pink, (b) (4) homogenous suspension when mixed (i.e., after shaking the bottle for at least 30 seconds). The product is supplied as a 140 mL suspension in a 150 mL amber PET bottle closed with a (b) (4) HDPE child proof screw cap with LDPE (b) (4) syringe adapter). Intended for multidose use.

- Drug product composition –

Ingredient	Content per mL	Function
Givinostat hydrochloride monohydrate (ITF2357)	10 mg	API
Polysorbate 20	(b) (4)	
Glycerin (b) (4)		
Tragacanth (b) (4)		
Sodium benzoate		
Peach flavor		
Cream flavor		

Saccharin sodium	(b) (4)
Non crystallizing Sorbitol Solution (b) (4) (b) (4)	
Tartaric acid	
Sodium hydroxide	
Purified water	

Sodium benzoate is (b) (4) The drug product pH release specification is (b) (4) shelf life specification is (b) (4)

Exhibit batch size: (b) (4) L, ~ (b) (4) bottles.
Maximum proposed commercial batch size: Same, (b) (4) L, ~ (b) (4) bottles.

- Description of container closure system –

Configuration	Component	Description	Manufacturer
140 mL fill in 150 mL bottle	Bottle	150 mL Amber PET bottle	(b) (4)
	Closure	(b) (4) child proof HDPE screw cap with LDPE (b) (4) syringe adapter)	

The bottle is co-packaged with (b) (4) and one 5 mL graduated oral dispenser (oral syringe). The oral dispensers are manufactured by (b) (4)

Assessment: **Adequate**

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

10 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Helen Ngai

Digitally signed by Helen Ngai
Date: 7/25/2023 11:56:23AM
GUID: 508da70b00028e6d6f228f597b070551

Elizabeth Bearr

Digitally signed by Elizabeth Bearr
Date: 7/25/2023 11:56:54AM
GUID: 55370d1e00cfd67fc04d8bfbedbf3096

CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	NDA 217865-Orig-1
Assessment Cycle Number	01
Drug Product Name/ Strength	DUVYZAT™ (Givinostat Hydrochloride Monohydrate) Oral Suspension 10 mg/mL
Route of Administration	Oral
Applicant Name	Italfarmaco S.p.A.
Therapeutic Classification/ OND Division	Histone deacetylase inhibitor /DN1
RLD/RS Number	N/A
Proposed Indication	Treatment of Duchenne Muscular Dystrophy
Primary Reviewer	Hansong Chen, PharmD, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: **Adequate**

Assessment Summary:

Italfarmaco S.p.A. developed DUVYZAT™ (Givinostat Hydrochloride Monohydrate) oral suspension 10 mg/mL and submitted this NDA on 4/21/2023 to seek approval through the 505(b)(1) regulatory pathway. The proposed indication is for the treatment of Duchenne Muscular Dystrophy.

The Biopharmaceutics review focused on the evaluation of the adequacy of the overall information/data pertaining to the proposed dissolution method and acceptance criterion.

Key findings of the Biopharmaceutics assessment:

The proposed dissolution method and acceptance criterion:

The Applicant's proposed dissolution method [USP Apparatus II (Paddle) at 30 rpm; 500 mL of pH 4.5 phosphate buffer at 37 °C] is acceptable. The proposed dissolution method was demonstrated to be discriminatory toward variations in PSD of drug substance and viscosity of drug product.

The proposed acceptance criterion of Q=(b)(4)% in (b)(4)minutes was tightened to "Q=(b)(4)% in 15 minutes", based on the provided dissolution profiles of clinical/registration batches and demonstrated discriminating ability of the method. The agreement to the recommended acceptance criterion was reached with the Applicant.

Recommendation:

From a Biopharmaceutics perspective, NDA 217865 for DUVYZAT™ (Givinostat Hydrochloride Monohydrate) oral suspension 10 mg/mL is **ADEQUATE**.
FDA-approved dissolution method and acceptance criterion:

USP Apparatus	Speed (RPMs)	Medium /Temperature	Volume (mL)	Acceptance Criterion
II (Paddle)	30	phosphate buffer pH 4.5 / 37 °C ± 0.5°C	500	Q= (b)(4)% in 15 minutes

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Sequence 0003 /Original submission	4/21/2023
Sequence 0020 /Response to Biopharmaceutics IR 1	8/11/2023
Sequence 0027 /Response to Biopharmaceutics IR 2	9/6/2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A
Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Assessment:
No BCS designation was requested. The Applicant reported that givinostat (ITF2357) is a BCS Class III drug substance. The solubility data show that givinostat is highly soluble across the physiological pH range (pH 1.2 – 6.8; Table 1). The Applicant conducted in vitro Caco-2 cell and MDCKII-MDR1 cell permeability studies and the results indicate that givinostat is poorly permeable.

Solubility:

Table 1. Solubility of givinostat in various aqueous media at 37 °C

	HCl 0.1 M, pH 1	Acetate buffer, pH 4.5	Phosphate buffer, pH 4.5	Phosphate buffer, pH 6.8
Experiment 1	0.32 mg/mL	5.11 mg/mL	5.77 mg/mL	0.88 mg/mL
Experiment 2	0.32 mg/mL	5.11 mg/mL	5.87 mg/mL	0.90 mg/mL
Experiment 3	0.31 mg/mL	5.08 mg/mL	5.86 mg/mL	0.89 mg/mL
Average	0.32 mg/mL	5.10 mg/mL	5.83 mg/mL	0.89 mg/mL
ITF2357 calculated amount that would be soluble in 250 mL of aqueous buffer based upon above average solubility data	80 mg	1275 mg	1458 mg	222.5 mg

Reviewer's comment:
The solubility data in Table 1 show that Givinostat (ITF2357) is highly soluble per BCS criteria as less than 250 mL of aqueous solution is needed to dissolve 70 mg of Givinostat (ITF2357) across the physiological pH range.

Permeability:

Table 2. Summary of Caco-2 and MDCKII-MDR1 Permeability Results for Givinostat (ITF2357)

Cell line	Papp A ⇒ B (10^{-6} cm /sec)	Papp B ⇒ A (10^{-6} cm /sec)	Papp A ⇒ B + P-gp inhibition (10^{-6} cm /sec)	Papp B ⇒ A+ P-gp Inhibition (10^{-6} cm /sec)
CaCo2 (21 day) (1)	2.31	56.6	12.4 (+Ver)	27.3 (+Ver)
CaCo2 (3 day) (2)	3.0	21.5	4.9 (+CsA)	10.0 (+CsA)
MDCKII-MDR1 (2)	5.3	21.3	15.7 (+CsA)	7.3 (+CsA)

Ver = Verapamil 100 µM
CsA = Cyclosporin A 10 µM

The Applicant conducted in vitro studies with the Caco-2 TC7 monolayer in a 21-day model and MDCKII-MDR1 cell model to determine the bidirectional permeability of Givinostat (ITF2357). Per the Applicant, data indicate that givinostat had low to medium absorptive permeability in Caco-2 cell monolayers and MDCKII-MDR1 cell.

Reviewer's comment:
The in vitro permeability studies were conducted with limited model drugs; thus, a definitive conclusion cannot be drawn with respect to the criteria for the BCS of permeability.

Dissolution: The dissolution data show that the proposed Givinostat Hydrochloride Monohydrate oral suspension can achieve a complete dissolution within 15 minutes in the proposed dissolution medium (i.e., pH 4.5 phosphate buffer) (see **Section B.2**).

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: ***{Adequate}***

1. Dissolution Method

Table 3. The proposed dissolution method and acceptance criterion for the prosed product

USP Apparatus	Speed (RPMs)	Medium /Temperature	Volume (mL)	Acceptance Criterion
II (Paddle)	30	pH 4.5 phosphate buffer / 37 °C ± 0.5°C	500(495 mL medium + 5 mL sample)	Q= (b) (4)% in (b) (4) min

1) Dissolution method development

(b) (4)

[redacted]

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

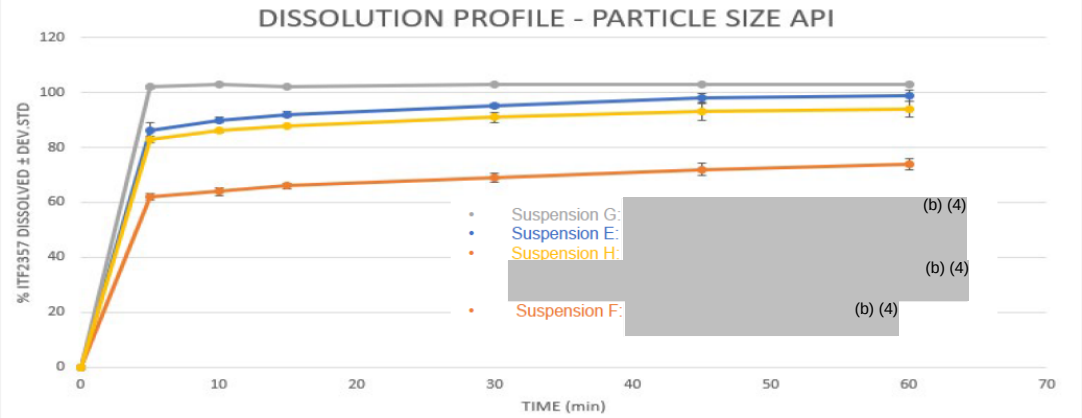
2) Discriminating power of the dissolution method

a) Effect of drug substance PSD on dissolution

The Applicant explored the discriminating power of the dissolution method towards the change in drug substance particle size distribution (PSD) by intentionally manufacturing different variant batches containing different PSDs. Suspension E is the reference/target formulation, which has PSD with D_{90} < (b) (4) µm. The Applicant proposed the specification for API PSD:

D_{90}: NMT (b) (4) µm
D_{50}: NMT (b) (4) µm
D_{10}: NMT (b) (4) µm

Figure 3. Dissolution profiles of givinostat oral suspension with different particle size API



As shown in Figure 3, the proposed dissolution method could discriminate the changes in API PSD. Additionally, the (b) (4) the particle size was, the (b) (4) the dissolution rate was observed.

b) Effect of drug product viscosity on dissolution

The Applicant explored the discriminating power of the dissolution method towards the change in the viscosity of the proposed drug by intentionally manufacturing variant batches with lower or higher percentage of (b) (4) The composition of reference and variant batches is shown in Table 5. Suspension E is the reference/target formulation, which has a viscosity of (b) (4) cp. The dissolution results are presented in Figure 4, which demonstrate that the proposed dissolution method can differentiate the changes in viscosity. Figure 4 shows that the higher viscosity leads to slower dissolution profiles.

Figure 4. Dissolution profiles of variant batches with different viscosity

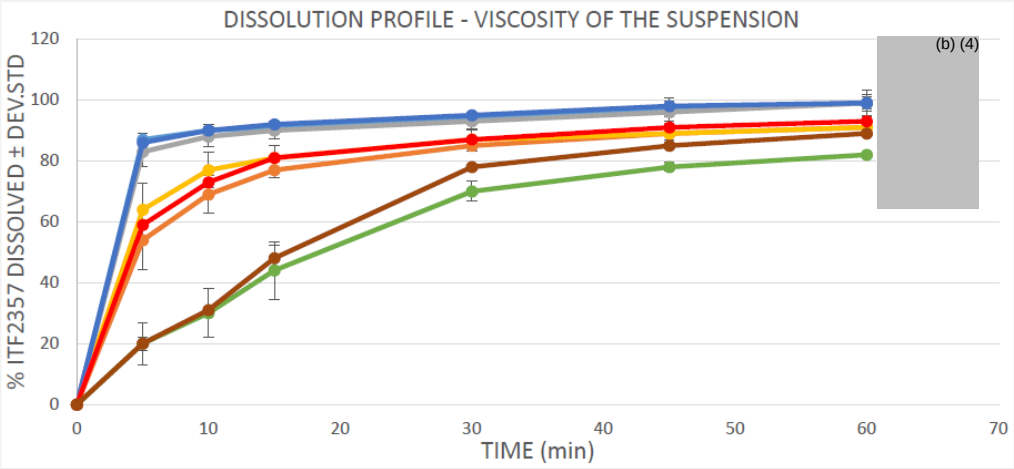


Table 5. Composition of variant batches with different viscosity

Ingredients	Composition for 100 mL (% w/v)							
	A	C	E	D	L	B	M	I
ITF2357	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
(b) (4)								
Viscosity (cP) (*)	(b) (4)							

Reviewer's overall comment on the dissolution method:
The proposed dissolution method discriminates towards changes in drug substance PSD and the viscosity of the final drug product. Tightening the dissolution acceptance criterion from "Q=(b) (4)% in (b) (4) min" to "Q=(b) (4)% in 15 min can reject certain variant batches as illustrated (Figures 3 and 4). Overall, the proposed dissolution method is deemed acceptable.

2. Dissolution Data and Acceptance Criterion

a) Dissolution data

The Applicant provided detailed information and complete dissolution profile data of 7 clinical and stability batches for the proposed drug product (Table 6). No release profile dissolution data are available for Clinical Batches 17002, 18001, and 20001. All batches have been produced at Italfarmaco SA (Spain) and are representative of the proposed commercial manufacturing process.

Table 6. List of all pivotal clinical and registration batches

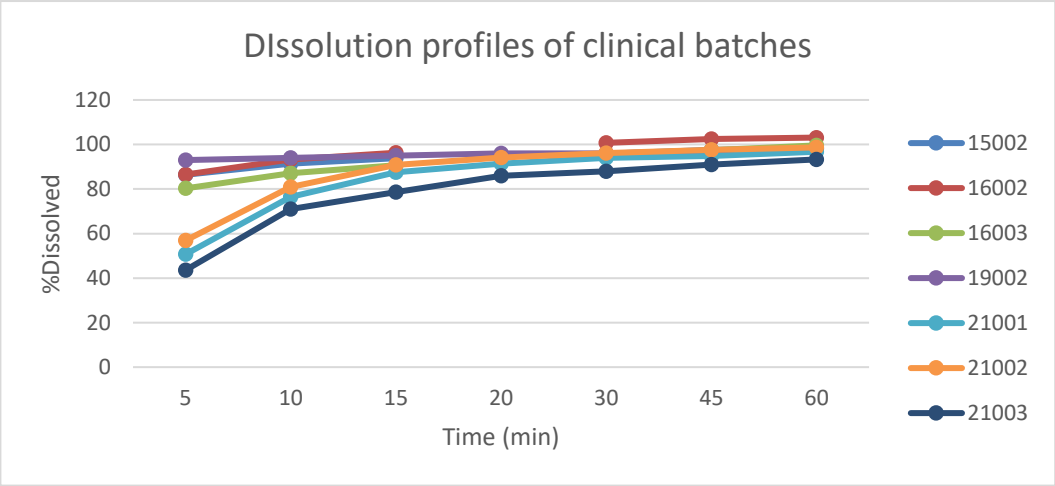
Batch number	Manufacturing date	Batch Size	Use
15002	April 2015	(b) (4) L	DSC/11/2357/43; DSC/14/2357/48; DSC/14/2357/51; stability
16002	July 2016	L	DSC/14/2357/48; DSC/14/2357/51; DSC/15/2357/53; stability
16003	July 2016	L	DSC/14/2357/48; DSC/14/2357/51; DSC/15/2357/53; stability
17002	November 2017	L	DSC/14/2357/48; DSC/14/2357/51; DSC/15/2357/53; stability
18001	December 2018	L	DSC/14/2357/51; Stability
19002	November 2019	L	DSC/14/2357/48; DSC/14/2357/51; ITF/2357/54; stability
20001	November 2020	L	DSC/14/2357/51; ITF/2357/55; stability
21001	June 2021	L	Clinical Study DSC/14/2357/51; stability
21002	June 2021	L	Clinical Study DSC/14/2357/51; stability
21003	June 2021	L	Clinical Study DSC/14/2357/51; stability

Table 7. Mean dissolution profile data of pivotal clinical and stability batches

Batch number/time(min)	5	10	15	20	30	45	60
15002	86.4	91.4	93.8	ND	95.8	97.6	98.3
16002	86.5	93.2	96.3	ND	100.8	102.5	103.1
16003	80.3	87.1	90.7	ND	95.0	97.4	99.6
19002	93	94	95	96	96	97	98
21001	50.71	76.46	87.56	91.36	93.98	94.91	96.74
21002	56.90	80.94	90.78	94.17	96.13	97.60	98.68
21003	43.58	70.96	78.65	85.89	87.96	90.99	93.29

ND- not determined

Figure 5. Mean dissolution profiles of clinical and stability batches



In Page 15 of Module 3.2.P.5.2 Analytical Procedures, the Applicant reported how it prepares samples for dissolution testing as follow:

Manually shake the ITF2357 oral suspension 10 mg/mL for at least 30 seconds by rotating the bottle by 180º and fill 6 graduated syringes with 5 mL of suspension. Weigh the syringes and register exact weight.

It seems that the Applicant takes all of six testing samples from a single bottle. For an oral suspension drug product, we expect that samples be taken from different bottles for dissolution testing. In Biopharmaceutics IR 1, we requested the Applicant to clarify whether it prepared and administered all the 5-mL testing samples into vessels from a single bottle to generate the dissolution profile data. If this is not how it was done, the Applicant should repeat the dissolution tests based on the requirement and generate complete dissolution profile data (n=12/batch) for all pivotal/clinical and registration batches.

In the IR response, the Applicant confirmed that the 5-mL dissolution testing samples have been administered from a single bottle because no specific requirements about number of bottles to be used for dissolution test have been found in USP or FDA guidance for the specific pharmaceutical form, oral suspension, supplied in a multidose bottles. The Applicant could not repeat dissolution testing for all clinical batches because most of them are already expired. However, no concerns have been raised during development on a possible intra-batch homogeneity or bottle to bottle variability due to the following reasons:

- In the dissolution tests performed on all pivotal clinical and registration batches during the whole development of the Givinostat Oral Suspension, the RSD% values were found very low, generally below 5% at 15 minutes and below 10% at later timepoints. According to USP <1092> greater than 10% is considered as highly variable for timepoints later than 10 minutes.
- Dissolution data were generated for the three submission batches 21001, 21002, and 21003 on 12 vessels by sampling from different bottles, specifically, 6 vessels sampled from 6 different bottles stored inverted + 6 vessels sampled from 6 different bottles stored upright for the 24 months stability timepoint at 25°C/60%RH. These data generated on different pivotal clinical batches confirm the low intra and inter batches variability.

Therefore, the Applicant concluded that the large amount of the dissolution data generated confirms low variability associated to sampling from different bottles and the suitability of the proposed dissolution method sampling from one single bottle.

Reviewer's comment:
Since dissolution data provided indicate that intra-bottle and inter-bottle dissolution has similar variability, this Reviewer concludes that all dissolution data obtained from the same bottles per batch are acceptable.

b) Dissolution acceptance criterion

The Applicant proposed the following dissolution acceptance criterion:
Q=(b)(4)% in (b)(4)minutes

Reviewer's comment:
Table 7 shows that all clinical/registration batches have a mean dissolution of at least (b) (4)% at 15 minutes, (b) (4) of dissolution at 15 minutes. The data indicate that the proposed dissolution acceptance criterion is liberal and can be tightened as follows: Q= (b) (4)% in 15 minutes. The study of the discriminating power of the proposed dissolution method further supports this Reviewer's decision. Setting an acceptance criterion of "Q= (b) (4)% in 15 minutes" can reject variant batches pertaining to viscosity and API PSD (see Figure 3 and Figure 4, respectively). The Biopharmaceutics IR 2 sent to the Applicant to convey the recommended dissolution acceptance criterion and the Applicant's agreement are presented in ***Appendix****.*

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA (PBBM modeling)

Assessment: *N/A*

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: *N/A*

BB.12 BRIDGING OF FORMULATIONS

Assessment: *N/A*

The to-be-marketed formulation is identical to the one used in clinical studies, thus no additional (in vitro or in vivo) bridging is needed between the two.

B. 13 BIOWAIVER REQUEST

Assessment: *N/A*

Appendix

Biopharmaceutics Information Requests and Applicant's Responses

Information Request 1 (dated 7/27/2023):

(b) (4)

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

The Applicant's response can be retrieved by clicking the following links:
\\CDSESUB1\EVSPROD\nda217865\0027\m1\us\12-cover-letters\cover-letter.pdf

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

Hansong Chen

Digitally signed by Hansong Chen
Date: 9/07/2023 03:38:21PM
GUID: 525d7d660003845a197a2e1682433d0d

Ta-Chen Wu

Digitally signed by Ta-Chen Wu
Date: 9/07/2023 04:00:48PM
GUID: 508da6df000269e151ff37cd8f4e13a1

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/

MARTHA R HEIMANN
09/26/2023 05:10:04 PM