CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213535Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval

NDA 213535
Review #1

Drug Product Name	Evrysdi (risdiplam)
Dosage Form	For oral solution
Strength	60 mg for 0.75 mg/mL solution
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Genentech Inc.
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Rohit Tiwari	Suong Tran
Drug Product	Andrei Ponta	Julia Pinto
Manufacturing	Sydney Choi	Nallaperumal Chidambaram
Microbiology	Yan Zheng	Elizabeth Bearr
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Dahlia Walters / Kelly Ballard	
Application Technical Lead	Martha Heimann	
Quality Surveillance	Luis Carrion	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

Submission(s)	Document Date	Discipline(s) Affected
SD-3, Original NDA	9/17/2019	All
SD-6, Unsolicited amendment/stability	10/15/2019	Drug Substance, Drug Product
SD-8, Response to IR	11/8/2019	Microbiology
SD-10, Response to IR	11/22/2019	Microbiology
SD-17, Response to IR	1/29/2020	Microbiology

Submission(s)	Document Date	Discipline(s) Affected
SD-19, Response to IR	2/28/2020	Microbiology
SD-20, Labeling	2/28/2020	Drug Product
SD-21, Labeling	3/6/2020	Drug Product
SD-22, Response to IR	3/9/2020	Drug Product
SD-23, Response to IR	3/12/2020	Manufacturing
SD-24, Response to IR	3/31/2020	Microbiology
SD-26, Response to IR	4/7/2020	Manufacturing
SD-27, Response to IR	4/15/2020	Manufacturing

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	IV		(b) (4)	--	N/A	Adequate information in NDA
	III			----	N/A	Adequate information in NDA
	III				N/A	Adequate information in NDA

B. Other Documents: *IND, RLD, or sister applications*

Document	Application Number	Description
IND	128972	Development of risdiplam for treatment of spinal muscular atrophy
		(b) (4)

2. CONSULTS

None

Reference ID: 4606963

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The OPQ review team recommends **APPROVAL** of NDA 213535, EVRYSDI (risdiplam) for oral solution. The application, as amended, provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Spinal muscular atrophy (SMA) is a debilitating, and often fatal disease that impacts a multitude of patients from newborns to adults. Severity of SMA ranges from the most severe form (SMA1) to a mild form (SMA4). SMA1 is often is fatal in neonates and infants, whilst patients with SMA4 may have mild muscle weakness and a normal life expectancy. There are two approved treatments for SMA, Spinraza (nusinersen) and Zolgesma. Nusinersen is an antisense oligonucleotide that administered by intrathecal infusion. Zolgesma is a one-time gene therapy indicated for patients up to age 24 months.

The applicant, Genentech, has developed risdiplam, new molecular entity, as an oral dosage form for treatment of SMA. Risdiplam is a (b) (4) small molecule, survival of motor neuron 2 (SMN2) pre-mRNA splicing modifier. If approved, risdiplam would be the only oral treatment for SMA, and would allow for treatment of patients who are ineligible for treatment with Spinraza or Zolgesma. The product is formulated as a powder for oral solution to be constituted with Purified Water or Water for Injection by the pharmacist before dispensing. The proposed in-use period is 64 days, for constituted product stored at 5°C.

Key factors for the OPQ review include the robustness of the drug substance and drug product manufacturing processes given the applicant's short development timeline. For the drug substance, the comparability of two processes used to manufacture the primary registration batches to the proposed commercial process was a key concern. For the drug product, (b) (4)

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Proposed indication including intended patient population	Treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.
Duration of treatment	Chronic
Maximum daily dose	5 mg
Alternative methods of administration	None

B. Quality Assessment Overview

Note: NDA 213535 was reviewed as part of the ICH Q12 Established Conditions (EC) Pilot Program. The applicant proposed ECs for drug substance and drug product manufacture as part of the product lifecycle management plan. The ECs were evaluated by the respective reviewers and discussed with other OPQ stakeholders including OPPQ and OLDP. Refer to the Drug Substance and Manufacturing reviews for details.

Drug Substance: Adequate

The active ingredient, risdiplam, is a (b) (4) small molecule that is manufactured (b) (4) The drug substance is a light yellow or greenish-yellow powder that is soluble in acidic aqueous media.

Risdiplam is manufactured (b) (4) The applicant provided sufficient manufacturing process information. The manufacturing process consistently produces (b) (4) to ensure drug product manufacturability. Neither polymorphic form nor particle size are critical quality attributes for the drug product because the product is constituted with water to form an oral solution prior to dispensing.

Risdiplam is adequately characterized by standard analytical methods and the data supports the proposed structure. The proposed acceptance criteria for all specified related substances impurities (b) (4) the qualification threshold as per ICH Q3 A (NMT (b) (4) each). The applicant's manufacturing process, in-process controls, control of critical steps and the manufacturing process development data ensure that these impurities are maintained at the proposed criteria. Based on the applicant's risk assessment, elemental impurities resulting from (b) (4) used in the manufacturing process (b) (4) are adequately (b) (4) (b) (4) controlled per ICH Q3D. Residual solvents are controlled per ICH Q3C limits.

The applicant requested a retest period of (b) (4) months under the long-term condition of (b) (4). The provided stability data supports this retest period.

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Drug Product: Adequate

The proposed product is a powder containing 60 mg of risdiplam. It is to be reconstituted with purified water to yield an 80 mL clear, greenish yellow to yellow, multi-dose, oral solution (0.75 mg/mL risdiplam). In addition to the drug substance, the product contains compendial excipients (mannitol, isomalt, tartaric acid, sodium benzoate, (b) (4) PEG 6000, sucralose, ascorbic acid, and disodium edetate) and a strawberry flavoring. The primary container closure system consists of a round, amber glass bottle with a (b) (4) closure. Each bottle of powder for oral solution will be supplied with a press-in bottle adapter (PIBA) and oral/enteral syringes (two 6 mL syringes and two 12 mL syringes).

The proposed regulatory specification includes appropriate test for the powder and constituted solution, including appearance, assay, related substances, content uniformity, pH, assays for (b) (4) (ascorbic acid) and (b) (4) (sodium benzoate), and microbiological testing. Acceptance criteria for related substance are consistent with ICH Q3B identification and qualification thresholds for the maximum daily dose of 5 mg. Analytical procedures are adequately described and validated.

Based on stability data provided, the drug product has been granted a 24-month expiry when stored at controlled room temperature. The in-use stability data supports 64 days of storage under refrigerated conditions after constitution.

Based on the drug product control strategies, release data, and stability results, the proposed drug product is adequate.

Labeling: Adequate

The proposed labeling was deemed adequate with minor revisions that be implemented when labeling is finalized.

Manufacturing: Adequate

The manufacturing process for the commercial drug product involves (b) (4) The manufacturing process is deemed adequately controlled.

Microbiology: Adequate

The drug product is a nonsterile powder to be constituted with purified water or sterile water for injection (WFI). The in-use period after constitution is up to 64 days for solution stored at 2°C – 8°C. (b) (4) (b) (4)

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(b) (4)

All microbiological tests for batch release and stability testing are deemed suitable for quality control.

Environmental Assessment: Adequate

The applicant claims a categorical exclusion under 21 CFR 25.31(b). Approval of the NDA will increase the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. The applicant indicates that no extraordinary circumstances are known to exist. The EIC calculation was not provided; however, based on incidence of SMA (10,000 – 25,000 patients in US) and proposed maximum dose, annual production. Per discussion with Jim Laurenson (EA Team) no further review is needed and the claim is granted.

Quality Surveillance: Adequate

The firm has a Pharmaceutical Quality System (PQS) framework in place to manage and control changes of the drug product.

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C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Assay/Stability	x Formulation x Container Closure x Process Parameters	**L**	(b) (4)	**Adequate**	
Uniformity of dose	x Formulation x Container Closure x Process Parameters	**M**		**Adequate**	(b) (4)
Physical stability (solid state)	x Formulation x Raw Materials x Process Parameters	**L**		**Adequate**	
Palatability	x Formulation x Raw Materials	**M**		**Adequate**	
Microbial limits	x Formulation x Raw materials x Process parameters x Scale/Equipment/Site	**L**		**Adequate**	

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D. List of Deficiencies for Complete Response

N/A

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D. 5/8/2020

Reference ID: 4606963

Martha Heimann

Digitally signed by Martha Heimann
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LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [TRADENAME] safely and effectively. See full prescribing information for [TRADENAME].

[TRADENAME]™ (risdiplam) powder, for oral solution
Initial U.S. Approval: 20XX

INDICATIONS AND USAGE

[TRADENAME] is a survival of motor neuron 2 (SMN2) splicing modifier indicated for the treatment of spinal muscular atrophy (SMA) in (b) (4) (b) (4) patients. (1)

DOSAGE AND ADMINISTRATION

[TRADENAME] must be constituted by a pharmacist prior to dispensing. Administer orally once daily using the provided oral syringe. (2.2)

Age	Recommended Daily Dose
2 months to < 2 years of age	0.20 mg/kg
≥ 2 years of age (< 20 kg)	0.25 mg/kg
≥ 2 years of age (≥ 20 kg)	5 mg

See Full Prescribing Information for important preparation and administration instructions. (2.3, 2.4)

DOSAGE FORMS AND STRENGTHS

(b) (4)

CONTRAINDICATIONS

(b) (4)

ADVERSE REACTIONS

(b) (4)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: XX/20XX

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	(risdiplam) powder for oral solution
Dosage form, route of administration	Powder for oral (b) (4)
Controlled drug substance symbol	Not applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	60 mg, constituted to 0.75 mg/mL

Is the information accurate? ☒ Yes ☐ No

2. *Section 2 Dosage and Administration*

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

(b) (4)

[TRADENAME] is taken orally once daily, at approximately the same time each day, (b) (4) (b) (4) (b) (4) If the patient is unable to swallow and has a nasogastric or gastrostomy tube, administer [TRADENAME] via the tube. The tube should be flushed with water after delivering [TRADENAME] *[see INSTRUCTIONS FOR USE]*.

It is recommended a health care provider discuss with the patient or caregiver how to prepare the prescribed daily dose prior to administration of the first dose *[see DOSAGE AND ADMINISTRATION (2.4)]*.

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2.2 Dosing Information

(b) (4)

The recommended (b) (4) is determined by age and body weight (see TABLE 1).

Table 1 Dosing Regimen by Age and Body Weight

Age	Recommended Daily Dose
2 months to < 2 years of age	0.20 mg/kg
≥ 2 years of age (< 20 kg)	0.25 mg/kg
≥ 2 years of age (≥ 20 kg)	5 mg

(b) (4)

Missed Dose

If a dose of [TRADENAME] is missed, administer as soon as possible if still within 6 hours of the missed dose. (b) (4)

(b) (4)

If a dose is not fully swallowed or vomiting occurs after taking a dose of [TRADENAME], (b) (4) (b) (4) to make up for the lost dose. Wait until the next day to take the next dose at the regularly scheduled time.

(b) (4) **Preparation of Oral Solution by Pharmacists**

[TRADENAME] powder must be constituted to the oral solution by a pharmacist prior to dispensing to the patient.

Preparation of (b) (4) Oral Solution (0.75 mg/mL)

The [TRADENAME] "Instructions for Constitution" booklet contains more detailed instructions on the preparation of the oral solution *[see INSTRUCTIONS FOR CONSTITUTION]*.

(b) (4)

(b) (4) Wear disposable gloves during the preparation and clean up procedure.

(b) (4)

1. Gently tap the bottom of the closed glass bottle to loosen the powder.
2. Remove the cap. Do not throw away the cap.
3. Carefully pour 79 mL of purified water into the [TRADENAME] bottle to yield the 0.75 mg/mL oral solution.
4. Insert the Press-In bottle adapter into the bottle opening by pushing it down against the bottle lip. Ensure it is completely pressed against the bottle lip.
5. Re-cap the bottle tightly and shake well for 15 seconds. Wait for 10 minutes. You should have obtained a clear solution. (b) (4) well again for another 15 seconds.
6. (b) (4)

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7. Put the bottle back in its original carton (b) (4)
8. Dispense with the "Instructions for Use" and FDA-approved patient labeling. Alert patients to read the important handling information described in the Instructions for Use.

(b) (4)

(36°F to 46°F). Do not freeze. Discard any unused portion 64 days after constitution.

Table 2 Selecting Oral Syringe for the Prescribed Daily Dose of [TRADENAME]

Dose Strength	Syringe Size	Dosing Volume	Syringe Increments
0.75 mg/mL (b) (4)	6 mL	1.0 mL to 6.0 mL	0.1 mL
	12 mL	6.2 mL to 6.6 mL	0.2 mL

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation	The powder must be reconstituted using 79 mL of water prior to administration.

Is the information accurate? ☒ Yes ☐ No

3. *Section 3 Dosage Forms and Strengths*

3 DOSAGE FORMS AND STRENGTHS

[TRADENAME] for oral solution: 60 mg. (b) (4)

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Risdiplam for oral solution
Strengths: in metric system	60 mg, constituted to 0.75 mg/mL
Active moiety expression of strength with equivalence statement	Not applicable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	The constituted solution is greenish yellow to yellow in color.

Is the information accurate? ☒ Yes ☐ No

4. *Section 11 Description*

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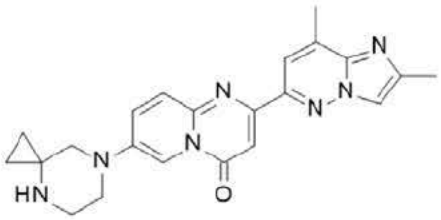
11 DESCRIPTION

[TRADENAME] (risdiplam) is a survival of motor neuron 2 (SMN2) splicing modifier.

[TRADENAME] is supplied as a powder in an amber glass bottle. Each bottle contains 60 mg of risdiplam. The powder is constituted with purified water to yield (b) (4) 60 mg/80 mL (0.75 mg/mL) of risdiplam, the active component. (b) (4) (b) (4)

The chemical name of risdiplam is 7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8 dimethylimidazo[1,2-b]pyridazin-6- yl)pyrido-4H-[1,2-a]pyrimidin-4-one.

The molecular formula of risdiplam is $C_{22}H_{23}N_7O$ and the chemical structure is shown below.



The inactive ingredients of [TRADENAME] are: ascorbic acid, disodium edetate dihydrate, isomalt, mannitol, polyethylene glycol 6000, sodium benzoate, strawberry flavor, sucralose, and tartaric acid.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Risdiplam powder for oral solution Reviewer's Note: Applicant will be asked to include the established name.
Dosage form and route of administration	Powder for oral solution
Active moiety expression of strength with equivalence statement (if applicable)	60 mg, constituted to 0.75 mg/mL
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Ascorbic acid, disodium edetate dihydrate, isomalt, mannitol, polyethylene glycol 6000, sodium benzoate, strawberry flavor, sucralose, and tartaric acid.
Statement of being sterile (if applicable)	Not Applicable
Pharmacological/ therapeutic class	Survival of motor neuron 2 (SMN2) splicing modifier
Chemical name, structural formula, molecular weight	$C_{22}H_{23}N_7O$, MW = 401.46 g/mol

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If radioactive, statement of important nuclear characteristics.	Not Applicable
Other important chemical or physical properties (such as pKa or pH)	Not Applicable

Is the information accurate? ☒ Yes ☐ No

5. ***Section 16 How Supplied/Storage and Handling***

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

How Supplied

Each amber glass bottle of [TRADENAME] is packaged with a bottle adapter (b) (4) (b) (4)

16. (b) (4) Storage and Handling

(b) (4) store the dry powder at (b) (4) at 20°C to 25°C (68°F to 77°F) [see USP controlled room temperature] and keep in the original carton.

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	60 mg, constituted to 0.75 mg/mL
Available units (e.g., bottles of 100 tablets)	Amber glass bottle packaged with a bottle adapter and oral syringes. 0.75 mg/mL risdiplam oral solution after constitution with 79 mL of water
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC number is provided Reviewer's Note: Applicant will be asked to include the color of the drug product
Special handling	After constitution, store the oral solution in a refrigerator between 2°C to 8°C (36°F to 46°F) for up to 64 days. Do not freeze. Keep the oral solution bottle

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	always in an upright position with the cap tightly closed
Storage conditions	Store the dry powder at room temperature, at 20°C to 25°C (68°F to 77°F) [see USP controlled room temperature] and keep in the original carton.
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Genentech, Inc

Reviewer's Assessment of Package Insert: ***Adequate***

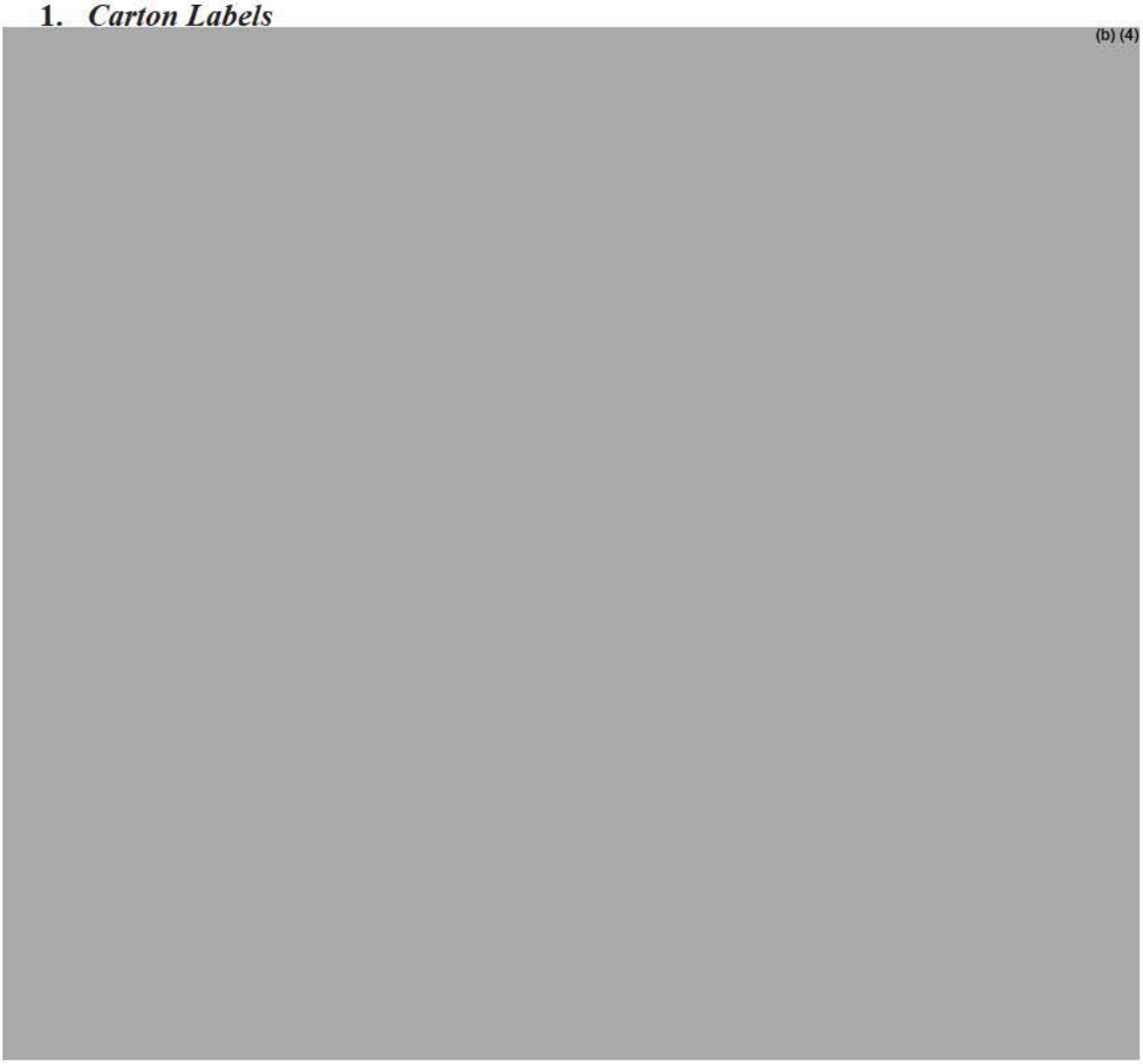
Prescribing Information complies with all regulatory requirements from a CMC perspective.

However, some revisions have been identified and will be communicated to the Applicant as part of DNP labeling negotiations.

II. Labels:

1. ***Carton Labels***

(b) (4)



Reference ID: 4606963

2. ***Bottle Label***

Item	Information provided in the pouch label
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Risdiplam powder for oral solution
Dosage strength	Reviewer's Note: Applicant will be asked to update the strength to reflect the amount of risdiplam in the powder (60 mg).
Net contents	Reviewer's Note: Applicant will be asked to update the strength to reflect the amount of risdiplam in the powder (60 mg).
"Rx only" displayed prominently on the main panel	Complies
NDC number (21 CFR 207.35(b)(3)(i))	Complies
Lot number and expiration date (21 CFR 201.17)	Complies
Storage conditions	Complies
Bar code (21CFR 201.25)	Complies
Name of manufacturer/distributor	Complies
And others, if space is available	Not Applicable

Reviewer's Assessment of Labels: ***Adequate***

The container labels comply with regulatory requirements from a CMC perspective. It bears the "Rx only" statement, the NDC number, name of manufacturer, net contents, strength, and the name (proprietary and established).

List of Suggested Edits Communicated to Applicant: Not Applicable

Overall Assessment and Recommendation: Adequate

Primary Labeling Reviewer Name and Date: Andrei Ponta

Reference ID: 4606963

Andrei Ponta

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Julia Pinto

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	213535
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Risdiplam powder for oral solution 0.75mg/mL
Route of Administration	Oral
Applicant Name	Genentech, Inc
Therapeutic Classification/ OND Division	OND/ODEI/DNP
Manufacturing Site	F. Hoffmann-La Roche Ltd. Grenzacherstrasse 124, 4070 Basel, Switzerland
Method of Sterilization	N/A for non-sterile

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
Original submission	09/17/2019
Amendment	10/15/2019
Response to IR	11/08/2019
Response to IR	11/22/2019
Response to IR	01/29/2020
Response to IR	02/28/2020
Response to IR	03/09/2020
Response to IR	03/31/2020

List Submissions being assessed (table):

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

Remarks:
This is eCTD submission. Submission dated 11/08/2019 is provided in response to the Agency's IR dated 10/30/2019. Submission dated 11/22/2019 is provided in response to the Agency's IR dated 11/14/2019. Submission dated 01/29/2019, 02/28/2020 and 03/31/2020 are provided in response to the Agency's IR dated 01/23/2020. Submission dated 03/09/2020 is provided in response to the Agency's IR dated 02/18/2020.
An updated product labeling is submitted on 03/06/2020. The revised labeling contains edits on the product name and clinical data, but the storage condition, instructions for constitution and instructions for use remain unchanged.

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Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): None

Supporting Documents: N/A

S DRUG SUBSTANCE

The manufacturing process for the drug substance is not reviewed because the drug substance is non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of the drug product:
The subject drug product is non-sterile powder for oral solution 0.75 mg/mL. Each bottle (b) (4) contains 60 mg of risdiplam. The powder

must be constituted with purified water to yield 80 mL clear oral solution and used as multiple-dose within 64 days.

Product composition:

Components	Reference to Standards	Function	Amount Bottle (mg/bottle)	Concentration in Solution per Bottle (mg/mL)
Risdiplam	In-house	Active ingredient	60.00	0.75
Mannitol[a]	USP, Ph. Eur., JP			
Isomalt	USP/NF, Ph. Eur., JP			
Strawberry Flavor[b,c]	In-house			
Tartaric Acid	USP/NF, Ph. Eur., JP			
Sodium Benzoate	USP/NF, Ph. Eur., JP			
(b) (4)	USP/NF, Ph. Eur., JP			
Polyethylene Glycol 6000				
Sucralose	USP/NF, Ph. Eur., JPE			
Ascorbic Acid	USP, Ph. Eur., JP			
Disodium Edetate Dihydrate	USP, Ph. Eur., JP			
Target Weight	—			
Target Volume[d]	—	—	—	80 mL

(b) (4)

(The picture is reproduced from the submission, 3,2,P.1, pg. 2).

Container closure system

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/s/

KELLY R BALLARD
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