CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219141Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 16, 2025

To: Christine Sadr, Sr. Regulatory Health Project Manager
Division of Cardiology and Nephrology (DCN)

Evan I. Fisher, M.D., Medical Officer (DCN)

Michael Monteleone, Associate Director for Labeling (DCN)

From: Charuni Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sapna Shah, Team Leader, OPDP

Subject: OPDP Labeling Comments for INZIRQO (hydrochlorothiazide), for oral suspension

NDA: 219141

Background:

In response to DCN's consult request dated June 5, 2024, OPDP has reviewed the proposed Prescribing Information (PI) for NDA under Section 505(b)(2) for INZIRQO (hydrochlorothiazide), for oral suspension

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on Friday, January 10, 2025 and are provided below.

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or charuni.shah@fda.hhs.gov.

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/s/

CHARUNI P SHAH
01/16/2025 12:03:11 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 27, 2024
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 219141
Product Name, Dosage Form, and Strength:	Inzirqo (hydrochlorothiazide) for oral suspension, 10 mg/mL
Applicant Name:	Novitium Pharma LLC
FDA Received Date:	December 20, 2024
TTT ID #:	2024-8963-1
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Novitium Pharma LLC submitted a revised container label received on December 20, 2024 for Inzirqo. We reviewed the revised container label for Inzirqo (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Novitium Pharma LLC implemented all of our recommendations and we have no additional recommendations at this time.

[a] Kundreskas, J. Label and Labeling Review for Inzirqo (NDA 219141). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 NOV 27. TTT ID: 2024-8963.

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/s/

JODY K KUNDRESKAS
12/27/2024 09:33:45 AM

NICOLE F IVERSON
12/27/2024 03:02:24 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	November 27, 2024
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 219141
Product Name, Dosage Form, and Strength:	Inzirqo (hydrochlorothiazide) for oral suspension, (b) (4) mg (b) (4) mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Novitium Pharma LLC
FDA Received Date:	March 28, 2024, September 11, 2024, and November 12, 2024
TTT ID #:	2024-8963
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 INTRODUCTION

As part of the approval process for Inzirqo (hydrochlorothiazide) for oral suspension, we reviewed the proposed Inzirqo Prescribing Information (PI), Patient Package Insert (PPI), and container label for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Inzirqo (hydrochlorothiazide) is a proposed 505(b)(2) drug product and the Listed Drug (LD) is Hydrodiuril (hydrochlorothiazide), NDA 011835. We note that NDA 011835 was Withdrawn FR Effective on July 8, 2011. As such, hydrochlorothiazide tablets under ANDA 083177 are the Reference Standard (RS).

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 219141.

Table 1. Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note that the proposed Inzirqo for oral suspension has the same active ingredient (hydrochlorothiazide), indications, recommended dosage, and route of administration as the Reference Standard (RS) hydrochlorothiazide. However, there are differences as the proposed product is for oral suspension, compared to tablets for the RS. The Applicant stated that the proposed oral suspension was developed to facilitate ease of dosing, in particular for patients who are elderly, have a preference for a liquid dosage form, and/or have difficulty swallowing and to provide clinicians with greater dosing flexibility within the approved dosage range compared to the currently marketed tablets and capsules.[a] Due to the change in dosage form, the strength differs (b) (4) mg/mL vs. (b) (4) 25 mg, and 50 mg). See Appendix A for full product characteristics comparison between the RS and the proposed product.

We note that the proposed product strength is (b) (4) mg (b) (4) mL, however adult doses range from 25 mg to 100 mg and pediatric doses are weight based. Therefore, we requested the Office of Pharmaceutical Quality (OPQ) review the strength presentation. OPQ stated that the proposed product strength should be revised to 10 mg/mL since some recommended doses are less than

[a] Clinical Overview of Hydrochlorothiazide Powder for Oral Suspension (NDA 219141). East Windsor (NJ): Novitium Pharma LLC; 2024 MAR 28. Available from: \\CDSESUB1\EVSPROD\nda219141\0001\m2\25-clin-over\25-clinical-overview-pdf.pdf.

(b) (4) mL. As this would be consistent with USP General Chapter <7>, we find this change acceptable.

The Applicant submitted revised Prescribing Information (PI) and container label shortening the reconstitution shaking time from (b) (4) to 30 seconds in response to an Information Request (IR) from OPQ.[b]

We performed a risk assessment of the proposed Prescribing Information (PI), Patient Package Insert (PPI), and container label to determine whether there are significant concerns in terms of safety related to preventable medication errors.

4 CONCLUSION

The proposed Inzirqo Prescribing Information (PI), Patient Package Insert (PPI), and container label may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Cardiology and Nephrology (DCN) in Section 5 and for Novitium Pharma LLC in Section 6.

5 RECOMMENDATIONS FOR THE DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Prescribing Information

1. Highlights of Prescribing Information
    a. The route of administration is missing. Failure to include the route of administration may lead to wrong route errors. Add the route of administration "orally" to each recommended dosage.
    b. The unit of measurement (e.g., mg/kg) does not follow each numeric value of dose for infants and children. This may lead to confusion and potential risk of wrong dose error. We recommend ensuring the unit of measure follows each numeric value for recommended dose. For example, revise "(b) (4) to "1 mg/kg to 2 mg/kg".
2. Section 2 Dosage and Administration
    a. The route of administration is missing. Failure to include the route of administration may lead to wrong route errors. Add the route of administration "orally" to each recommended dosage.
    b. The unit of measurement (e.g., mg/kg) does not follow each numeric value of dose for infants and children. This may lead to confusion and potential risk of wrong dose error. We recommend ensuring the unit of measure follows each numeric value for recommended dose. For example, revise "(b) (4) to "1 mg/kg to 2 mg/kg".

[b] Response to Information Request Letter (NDA 219141). East Windsor (NJ): Novitium Pharma LLC; 2024 NOV 12. Available from: \\CDSESUB1\EVSPROD\nda219141\0012\m1\us\12-ir-response-sequence0012.pdf.

c. The title of Section 2.5, *Important Administration Instructions*, is misleading as it contains information on preparation, and storage and handling of the reconstituted product. Unclear titles may contribute to important information being overlooked. Revise the title of Section 2.5 to *Preparation of Oral Suspension*.

d. As currently presented, the instruction that the powder should be prepared prior to dispensing is missing. This product is intended to be prepared by the pharmacy prior to dispensing. Not including this statement may result in the product being dispensed without reconstitution. Add the sentence "[TRADENAME] is supplied as a powder for oral suspension and must be reconstituted prior to dispensing." Underneath the heading of Section 2.5, *Preparation of Oral Suspension*. The statement (b) (4) can then be removed from the first bullet.

e. As currently presented, the information on post-reconstitution storage is missing. Including information on post-reconstitution storage will inform healthcare providers during product preparation and patient and caregivers after product preparation and minimize the risk of administering deteriorated drug products. Include information on post-reconstitution storage in Section 2.5, *Preparation of Oral Suspension* (b) (4) (b) (4) We recommend adding two bullets to the end of this section state:

- Store the reconstituted solution at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not freeze.
- Write the date of expiration of the reconstituted oral suspension (calculated as 30 days after reconstitution) on the bottle label.

f. As currently presented, instructions on how to measure the prescribed dose are missing. Failure to include all instructions may lead to confusion and risk of wrong dose error. We recommend adding an additional subsection, Section 2.6, *Important Administration Instructions* and adding the following statements to this section: "Instruct patients or caregivers to use an oral dosing syringe to correctly measure the prescribed amount of medication. Inform patients that a bottle adapter and oral dosing syringes may be obtained from their pharmacy.". We also recommend relocating the statements, "Advise patients to always shake the bottle well prior to each use." and "TRADENAME may be administered with or without food *[see Clinical Pharmacology (12.3)]*." to this section.

3. Section 3 Dosage Forms and Strengths
   a. The dosage form is not provided in Section 3. The dosage form is required per 21 CFR 201.57(c)(4). Add the dosage form in Section 3 in accordance with 21 CFR 201.57(c)(4).

4. Section 16 How Supplied/Storage and Handling

a. The storage and handling of the reconstituted solution should be described in Section 2, *Dosage and Administration*, rather than Section 16, *How Supplied/Storage and Handling*. Section 16 may include a summary statement with a cross-reference to the information in Section 2. We recommend revising Section 16.2, *Storage*, to:
"Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not freeze.

Keep this and all medication out of the reach of children.

Store reconstituted solutions of TRADENAME at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. *[see Dosage and Administration (2.5)]."*

5. Section 17 Patient Counseling
   a. As currently presented, some information in Section 17.5, *Recommended Administration* is not necessary to convey to patients during counseling. Providing unnecessary information to patients may result in confusion and medication errors. We recommend removing (b) (4) as this information is intended for the healthcare provider and is already located in Section 2.
   b. As currently presented, some instructions on how to store the reconstituted solution are missing from Section 17.5, *Recommended Administration.* Failure to include all instructions may lead to administration of deteriorated drug product. We recommend adding the following statement to this section: "Advise patients that the oral suspension should be stored at room temperature (20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)).".
   c. As currently presented, some instructions on how to measure the prescribed dose are missing from Section 17.5, *Recommended Administration.* Failure to include all instructions may lead to confusion and risk of wrong dose error. We recommend adding the following statement to the end of the fourth paragraph of this section: "Inform patients that a bottle adapter and oral dosing syringes may be obtained from their pharmacy.".

B. (b) (4)

(b) (4)

6 RECOMMENDATIONS FOR NOVITIUM PHARMA LLC

A. Container Label

1. As currently presented, the statement "Each (b) (4) mL) contains (b) (4) mg of hydrochlorothiazide, USP when reconstituted as directed." uses both the metric and apothecary systems of measurement and the strength does not match the strength in the Prescribing Information. We recommend expressing statement in metric units only and revising the strength to 10 mg/mL to be consistent with the Prescribing Information. Revise to "Each mL contains 10 mg of hydrochlorothiazide, USP when reconstituted as directed.".
2. As currently presented, the dosage form "for Oral Suspension" is displayed split on two lines. The dosage form statement for drug products should be located either on the same line as the active ingredient (established name) or directly below. Splitting the dosage form into two lines may increase the risk of the dosage form being misinterpreted as "Oral Suspension". We recommend presenting the proprietary name, established name, dosage form, and strength as:

   TRADENAME
   (hydrochlorothiazide)
   For Oral Suspension, USP
   10 mg/mL

   See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
3. As currently presented, the "Rx only" and net quantity statements appear prominent on the Principal Display Panel (PDP). The "Rx only" and net quantity statements should not compete in size and prominence with critical information on the PDP. We recommend reducing the prominence of the "Rx only" and net quantity statements so that they do not compete in size or prominence with critical information on the PDP. This can be accomplished by debolding and/or reducing the size of the statements. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
4. The terminology within the statement of dosage statement (i.e., (b) (4) (b) (4) is inconsistent with the terminology in the Prescribing Information. To ensure consistency with the terminology in the Prescribing Information, we recommend revising the statement of dosage statement to read, "Recommended Dosage: see Prescribing Information.".

5. The statement “Pharmacist: Must reconstitute before dispensing” is not present on the container label and/or carton labeling. This product is intended to be prepared by the pharmacy prior to dispensing. Not including this statement may result in the product being dispensed without reconstitution. We recommend adding the statement “Pharmacist: Must reconstitute before dispensing” on the PDP.
6. The bolded statement [redacted] (b) (4) is misleading as it contains information on storage and handling of the dry powder and prepared suspension. Unclear titles may contribute to important information being overlooked. We recommend revising this section to “Storage of Dry Powder and Suspension:”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Hydrochlorothiazide received on November 12, 2024 from Novitium Pharma LLC, and the Reference Standard (RS).

Table 2. Relevant Product Information for Hydrochlorothiazide and the Reference Standard (RS)

Product Name	**Hydrochlorothiazide**	**Hydrochlorothiazide**[c]
Initial Approval Date	N/A	February 24, 1959
Active Ingredient	(hydrochlorothiazide)	
Indication	Hypertension: alone or with other antihypertensive agents, to lower blood pressure. Edema: (b) (4) (b) (4) edema associated with congestive heart failure, hepatic cirrhosis and (b) (4) (b) (4) (b) (4) renal dysfunction, including nephrotic syndrome (b) (4) (b) (4)	As adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy. Has also been found useful in edema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure. Indicated in the management of hypertension, either as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs in the more severe forms of hypertension.
Dosage Form	for oral suspension	tablets
Strength	(b) (4)	(b) (4) 25 mg, and 50 mg
Route of Administration	Oral	

[c] Final Package Insert for Hydrochlorothiazide ANDA 083177. Parsippany (NJ): Ivax Pharmaceuticals Inc., an indirect, wholly owned subsidiary of Teva Pharmaceuticals USA, Inc.; 2009 APR 28. Available from: \\CDSESUB1\EVSPROD\anda083177\0040\m1\us\final-pi.pdf.

Table 2. Relevant Product Information for Hydrochlorothiazide and the Reference Standard (RS)		
Product Name	Hydrochlorothiazide	Hydrochlorothiazide[c]
Dose and Frequency	• Hypertension: (b) (4) is 25 mg daily given as a single dose. The dose may be increased to 50 mg daily, given as a single or two divided doses. (b) (4) (b) (4) • Edema in Adults: (b) (4) is 25 mg to 100 mg daily as a single or divided dose. (b) (4) (b) (4) intermittent therapy, i.e., administration on alternate days or on 3 to 5 days each week. • (b) (4) (b) (4) Hypertension): (b) (4) is (b) (4) to 2 mg/kg per day in single or two divided doses, not to exceed 37.5 mg per day in (b) (4) 2 years of age or 100 mg per day in children 2 to 12 years of age. In (b) (4) less than 6 months of age, doses up to 3 mg/kg per day in two divided doses may be required.	• Adults Edema: usual adult dosage is 25 mg to 100 mg daily as a single or divided dose. Many patients with edema respond to intermittent therapy, i.e., administration on alternate days or on 3 to 5 days each week. Hypertension: usual dose in adults is 25 mg daily given as a single dose. The dose may be increased to 50 mg daily, given as a single or two divided doses. • Infants and children Diuresis and control of hypertension: usual pediatric dosage is 0.5 mg to 1 mg per pound (1 to 2 mg/kg) per day in single or two divided doses, not to exceed 37.5 mg per day in infants up to 2 years of age or 100 mg per day in children 2 to 12 years of age. In infants less than 6 months of age, doses up to 1.5 mg per pound (3 mg/kg) per day in two divided doses may be required.

Table 2. Relevant Product Information for Hydrochlorothiazide and the Reference Standard (RS)		
Product Name	Hydrochlorothiazide	Hydrochlorothiazide[c]
How Supplied	An off-white to light-brown colored powder for oral suspension in one strength containing 800 mg of hydrochlorothiazide, USP in a HDPE bottle. When reconstituted as directed, TRADENAME forms an off-white to light brown colored suspension with caramel, peppermint flavor. The total volume of the suspension is 80 mL containing (b) (4) mg of hydrochlorothiazide, USP per (b) (4) mL (70954-522-10).	• (b) (4) • 25 mg tablets: bottles of 100 or bottles of 1000 tablets. • 50 mg tablets: bottles of 100 or bottles of 1000 tablets.
Storage	(b) (4) Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not freeze. Keep this and all medication out of the reach of children. (b) (4)	Dispense in a well-closed container as defined in the USP, with a child-resistant closure (as required). Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Keep this and all medications out of the reach of children.
Container Closure	(b) (4)	Bottles of 100, (b) (4) 1000 tablets.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Hydrochlorothiazide labels and labeling submitted by Novitium Pharma LLC.

- Prescribing Information and Patient Package Insert received on September 11, 2024, available from \\CDSESUB1\EVSPROD\nda219141\0008\m1\us\11413-draft-package-insert-pdf.pdf
- Container label received on September 11, 2024

B.2 Container Label Image

Container Label:

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX C. PREVIOUS DMEPA REVIEWS

On August 15, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, ‘hydrochlorothiazide” and “HCTZ”. Our search identified no previous reviews.

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/s/

JODY K KUNDRESKAS
11/27/2024 12:37:56 PM

NICOLE F IVERSON
11/27/2024 03:41:31 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of New Drugs
Office of Rare Diseases Pediatrics and Reproductive Medicine
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Division of Pediatrics and Maternal Health Memorandum

Date: 11/8/24 **Date Consulted:** 6/5/24

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
DPMH

To: Division of Cardiology Nephrology (DCN)

NDA: 219141

Drug: Inzirqo (hydrochlorothiazide) powder for oral suspension, (b) (4)

Proposed Indication: A diuretic and antihypertensive indicated for:

- The treatment of hypertension alone or with other antihypertensive agents, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarction.
- (b) (4) edema associated with congestive heart failure, hepatic cirrhosis, (b) (4)
- The treatment of edema (b) (4) including nephrotic syndrome, (b) (4)

Applicant: Novitium Pharma LLC

Subject: Pregnancy and Lactation Labeling Rule (PLLR)

Materials Reviewed:

- Prior DPMH PLLR labeling review for Dutoprol (metoprolol/hydrochlorothiazide) NDA 021956, by Jean Limpert, MD, dated 8/30/21, DARRTs Reference ID: 4849374.[1]
- Prior DPMH PLLR labeling review for Thalitone (chlorthalidone) NDA 19574, by Kristie Baisden, DO, dated 7/9/19, DARRTs Reference ID: 4465792.[1]
- Prior DPMH PLLR labeling review for Amturnide (aliskiren, amlodipine, hydrochlorothiazide), NDA 20045, by Miriam Dinatale, DO, dated 10/4/16, DARRTS Reference ID: 3994411.[1]

Consult Question: "DCN requests DPMH review the applicant's proposed PLLR labeling. We think this may be the first PLR/PLLR of a monotherapy hydrochlorothiazide."

INTRODUCTION

On March 28, 2024, the applicant, Novitium Pharma LLC, submitted a new NDA 219141 for Inzirqo (hydrochlorothiazide) powder for oral suspension using the 505(b)(2) regulatory. On June 5, 2024, the Division of Cardiology Nephrology (DCN) consulted the Division of Pediatrics and Maternal Health (DPMH) to assist with the labeling review for the *Pregnancy*, *Lactation,* and *Females and Males of Reproductive Potential* subsections.

BACKGROUND

Regulatory History

- Inzirqo (hydrochlorothiazide) NDA 219141 relies on the listed drug (LD) Hydrodiuril (hydrochlorothiazide) tablets NDA 011835. The LD was FDA approved in 1959 and discontinued from marketing in 2011 for reasons other than safety or effectiveness.
- The applicant established a clinical bridge by conducting comparative bioavailability (BA) studies with the reference standard (RS) hydrochlorothiazide (ANDA 083177), to support its reliance on the Agency's findings of safety and efficacy for the LD.
- Since initial FDA approval in 1959, 467 oral, single-entity and fixed-dose combination dosage forms of hydrochlorothiazide have been approved or tentatively approved.
- The proposed indication for Inzirqo (hydrochlorothiazide) powder for oral suspension is a diuretic and antihypertensive indicated for:
    - The treatment of hypertension alone or with other antihypertensive agents, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarction.
    - (b) (4) edema associated with congestive heart failure, hepatic cirrhosis, and (b) (4)
    - The treatment (b) (4) including nephrotic syndrome, (b) (4)

[1] The prior DPMH Reviews of Dutoprol NDA 021956, Thalitone NDA 19574, and Amturnide NDA 20045 were part of the materials reviewed for background purposes but was not a source relied upon for the labeling recommendations below.

Drug Characteristics[2]

- *Description:* diuretic and antihypertensive
- *Mechanism of action:* the mechanism of the antihypertensive effect of thiazides is unknown.
- *Dosage forms and strengths:* (b) (4)
- *Dosage and administration*:
    - For control of hypertension: usual initial dose is 25 mg daily. Dose may be increased to 50 mg daily. Doses above 50 mg are often associated with marked reductions in serum potassium and usually not required when used with other antihypertensive agents.
    - For edema in adults: usual dose is 25 mg to 100 mg daily. Many patients respond to intermittent therapy (3 to 5 days per week) which is less likely to result in electrolyte imbalance.
    - In infants and children: usual dose is 1 to 2 mg/kg per day, not to exceed 37.5 mg per day in infants up to 2 years of age or 100 mg per day in children 2 to 12 years of age. In infants less than 6 months of age, doses up to 3 mg/kg per day in two divided doses may be required.
- *Half-life:* 10 hours
- *Molecular Weight:* 297.74 grams/mol

Current State of the Labeling[2]

The listed drug (LD) Hydrodiuril (hydrochlorothiazide) tablets NDA 011835 was withdrawn from the market in 2011. The reference standard (RS) Hydrochlorothiazide tablets ANDA 083177 currently approved labeling does not conform to the content and format of the Physician Labeling Rule (PLR) or the Pregnancy and Lactation Labeling Rule (PLLR). Relevant pregnancy and lactation labeling for the RS is described below:

- **INDICATIONS**

  Use in Pregnancy

  Routine use of diuretics during normal pregnancy is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

  Edema during pregnancy may arise from pathologic causes or from the physiologic and mechanical consequences of pregnancy. Thiazides are indicated in pregnancy when edema is due to pathologic causes, just as they are in the absence of pregnancy (see PRECAUTIONS, Pregnancy). Dependent edema in pregnancy, resulting from restriction of venous return by the gravid uterus, is properly treated through elevation of the lower extremities and use of support stockings. Use of diuretics to lower intravascular volume in this instance is illogical and unnecessary. During normal pregnancy there is hypervolemia which is not harmful to the fetus or the mother in the absence of cardiovascular disease. However, it may be associated with edema, rarely generalized edema. If such edema causes discomfort, increased recumbency will often provide relief.

[2] Hydrochlorothiazide ANDA 08177 currently approved labeling.

Rarely this edema may cause extreme discomfort which is not relieved by rest. In these instances, a short course of diuretic therapy may provide relief and be appropriate.

- **PRECAUTIONS**
  Pregnancy
  Teratogenic Effects
  Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg hydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

  Nonteratogenic Effects
  Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

- **Nursing Mothers**
  Thiazides are excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue hydrochlorothiazide, taking into account the importance of the drug to the mother.

- **Carcinogenesis, Mutagenesis, Impairment of Fertility**
  Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 mg/kg and 4 mg/kg, respectively, prior to conception and throughout gestation.

REVIEW
PREGNANCY
Nonclinical Experience
No nonclinical reproductive toxicology studies were submitted.

Applicant's Review of Pharmacovigilance Database
The applicant noted that Novitium has not previously marketed hydrochlorothiazide in any country and does not maintain a pharmacovigilance database for hydrochlorothiazide. Further, no clinical studies were performed for this NDA submission.

Applicant's Review of Published Literature
The applicant submitted a review and summary of the available published literature regarding hydrochlorothiazide's use during pregnancy to support the proposed PLLR labeling for Inzirqo (hydrochlorothiazide). The literature review was conducted in MEDLINE (via PubMed) from August 20, 2020 (the last USPI modification date for the RS) until October 20, 2023. See the applicant's PLLR report submitted with this NDA for details regarding the

search strategy.[3] No new publications were identified regarding the safety of hydrochlorothiazide use during pregnancy.

DPMH's Review of Published Literature

DPMH most recently reviewed the published literature in 2021 regarding the safety of hydrochlorothiazide use during pregnancy.[4] Refer to this prior DPMH PLLR review for background information regarding Hypertension in Pregnancy and detailed literature review.

Briefly, DPMH noted that the 2019 American College of Obstetrics and Gynecology Practice Bulletin for Chronic Hypertension and Pregnancy states,

> "diuretics, like hydrochlorothiazide, generally are considered second-line agents for the treatment of hypertension in pregnancy. Theoretical concern has been raised regarding the potential for diuretics to cause intravascular volume depletion and thereby lead to fetal growth restriction or oligohydramnios; however, this concern is not supported based on data from a meta-analysis of nine randomized trials as well as systematic review of diuretics for the prevention of preeclampsia."

DPMH concluded hydrochlorothiazide does presently not appear to be commonly used during pregnancy. The available human data is from small observational studies largely from the 1960-1980s when diuretics were routinely prescribed to try to prevent or delay the development of preeclampsia. However, this practice was stopped because it was not effective and there was concern that the initial volume depletion caused by thiazides could reduce uteroplacental diffusion. During this time, there were rare reports that thiazides caused rare but serious adverse effects in exposed infants (such as jaundice, thrombocytopenia, and elective imbalances). Overall, no new interim safety data were identified by DPMH in 2021 from the prior 2016 DPMH PLLR review of hydrochlorothiazide that had not identified an increased risk of congenital malformations or miscarriage.[5] DPMH labeling recommendations maintained a statement for hydrochlorothiazide products that there are rare reports of jaundice, thrombocytopenia, and electrolyte imbalances in infants exposed to thiazide diuretics during pregnancy.

This Reviewer performed an interim search from the time of the last DPMH PLLR review for hydrochlorothiazide in 2021 to present in PubMed, Embase, Micromedex[6], TERIS[7], Reprotox[8], and Briggs[9] to find relevant articles not cited by the applicant. Search terms included "hydrochlorothiazide" AND "pregnancy," "pregnant women," "birth defects,"

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[3] Inzirqo (hydrochlorothiazide) NDA 219141 submission PLLR report, "Effects on hydrochlorothiazide on pregnancy, lactation, and reproductive potential."

[4]Prior DPMH PLLR labeling review for Dutoprol (metoprolol/hydrochlorothiazide) NDA 021956, by Jean Limpert, MD, dated 8/30/21, DARRTs Reference ID: 4849374.

[5] Prior DPMH PLLR labeling review for Amturnide (aliskiren, amlodipine, hydrochlorothiazide), NDA 20045, by Miriam Dinatale, DO, dated 10/4/16, DARRTS Reference ID: 3994411.

[6] Truven Health Analytics information, http://www.micromedexsolutions.com. Accessed 11/4/24.

[7]TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 11/4/24.

[8]Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 11/4/24.

[9] Briggs GG, et al. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, 9th Ed. 2011.

"congenital malformations," "stillbirth," "spontaneous abortion," OR "miscarriage." No new relevant epidemiological studies were identified.

LACTATION

Nonclinical Experience

No nonclinical lactation studies were submitted.

Applicant's Review of Pharmacovigilance Database

The applicant noted that Novitium has not previously marketed hydrochlorothiazide in any country and does not maintain a pharmacovigilance database for hydrochlorothiazide. Further, no clinical studies were performed for this NDA submission.

Applicant's Review of Published Literature

The applicant submitted a review and summary of the available published literature regarding hydrochlorothiazide's use during lactation to support the proposed PLLR labeling for Inzirqo (hydrochlorothiazide). The literature review was conducted in MEDLINE (via PubMed) from August 20, 2020 (the last USPI modification date for the RS) until October 20, 2023. See the applicant's PLLR report submitted with this NDA for details regarding the search strategy.[3] No new publications were identified regarding the safety of hydrochlorothiazide use during lactation or concentrations in human milk.

DPMH's Review of Published Literature

DPMH most recently reviewed the published literature in 2021 regarding the safety of hydrochlorothiazide use during lactation.[4] Refer to this prior DPMH PLLR review for detailed literature information. Briefly, DPMH noted that lactation literature was previously reviewed in 2016 including a case report describing breast milk and serum levels in a mother and breastfed infant exposed to hydrochlorothiazide as well as the use of hydrochlorothiazide to suppress lactation.[5] No interim lactation safety data was identified by DPMH in 2021. Labeling recommendations included a statement that hydrochlorothiazide is present in human milk, there are no reports of adverse effects on breastfed infants exposed to hydrochlorothiazide during lactation, and doses associated with clinically significant diuresis have been associated with impaired milk production.

This Reviewer performed a search from the time of the last DPMH PLLR review for hydrochlorothiazide in 2021 to present in *Medications and Mother's Milk*[10], LactMed[11], Micromedex[6], Reprotox[8], Briggs[9], PubMed, and Embase using the terms "hydrochlorothiazide" AND "lactation" OR "breastfeeding." No new relevant published literature was identified.

[10] Hale, Thomas (2017) Medications and Mother's Milk. Amarillo, Texas. Hale Publishing.

[11] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 11/4/24.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

No nonclinical fertility studies were submitted.

Applicant's Review of Pharmacovigilance Database

The applicant noted that Novitium has not previously marketed hydrochlorothiazide in any country and does not maintain a pharmacovigilance database for hydrochlorothiazide. Further, no clinical studies were performed for this NDA submission.

Applicant's Review of Published Literature

The applicant submitted a review and summary of the available published literature regarding hydrochlorothiazide's effect on male or female fertility to support the proposed PLLR labeling for Inzirqo (hydrochlorothiazide). The literature review was conducted in MEDLINE (via PubMed) from August 20, 2020 (the last USPI modification date for the RS) until October 20, 2023. See the applicant's PLLR report submitted with this NDA for details regarding the search strategy.[3] No new publications were identified regarding the effects of hydrochlorothiazide on male or female fertility.

DPMH's Review of Published Literature

DPMH most recently reviewed the published literature in 2021 regarding hydrochlorothiazide use and effects on male or female fertility.[4] No interim safety information was identified from the prior 2016 DPMH PLLR review which did not identify published literature regarding effects of hydrochlorothiazide on human fertility.[5]

This Reviewer performed a search from the time of the last DPMH PLLR review for hydrochlorothiazide in 2021 to present in PubMed, Embase, and Reprotox[8] using the terms "hydrochlorothiazide" AND "fertility," "contraception," "oral contraceptives," OR "infertility." No new relevant published literature was identified.

DISCUSSION and CONCLUSIONS

Pregnancy

Hypertension in pregnancy is associated with adverse effects on the mother and fetus and labeling will include clinical considerations regarding the adverse effects of the underlying disease. There are limited available human data regarding hydrochlorothiazide from small observational studies largely from the 1960s-1980s. Hydrochlorothiazide does not presently appear to be commonly used during pregnancy and there are no interim safety data to add to labeling from the most recent DPMH PLLR review in 2021.

Therefore, DPMH recommends subsection 8.1 of Inzirqo labeling include a statement that available data from published observational studies have not demonstrated a drug-associated risk of major birth defects or miscarriage with hydrochlorothiazide use during pregnancy. However, there have been rare reports of jaundice, thrombocytopenia, and electrolyte imbalances in infants exposed to thiazide medications during pregnancy.

Lactation
Hydrochlorothiazide is present in human milk and there is only one published case in the literature regarding maternal and infant levels. There are no reports of adverse effects on breastfed infants exposed to hydrochlorothiazide during lactation. Doses of hydrochlorothiazide associated with clinically significant diuresis have impaired milk production.

DPMH recommends subsection 8.2 of Inzirqo labeling including the following benefit/risk statement for use during lactation: "the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Inzirqo and any potential adverse effects on the breastfed infant from Inzirqo or from the underlying maternal condition."

Females and Males of Reproduction Potential
There are no pregnancy testing contraception recommendations to convey in labeling. There are no data to suggest hydrochlorothiazide adversely affects fertility. Therefore, DPMH recommends omitting subsection 8.3 of Inzirqo labeling.

LABELING RECOMMENDATIONS
DPMH revised subsection 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH discussed the PLLR labeling recommendations below with the DCN Review Team on November 8, 2024. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Hydrochlorothiazide Pregnancy and Lactation Labeling
FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Untreated hypertension during pregnancy can lead to adverse outcomes for the mother and the fetus *(see Clinical Considerations).* Available data from published observational studies have not demonstrated a drug-associated risk of major birth defects, miscarriage or adverse maternal outcomes with hydrochlorothiazide use during pregnancy. However, there have been rare reports of jaundice, thrombocytopenia, and electrolyte imbalances in infants exposed to thiazide medications during pregnancy.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations
Disease-Associated Maternal and/or Embryo/Fetal Risk
Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension (b) (4) monitored (b) (4) (b) (4)

Data

Animal Data

Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 mg/kg and 1000 mg/kg hydrochlorothiazide, respectively, provided no evidence of harm to the fetus.

8.2 Lactation

Risk Summary

Available data from published literature indicate hydrochlorothiazide is present in human milk *(see Data)*. There are no reports of adverse effects on breastfed infants exposed to hydrochlorothiazide during lactation. Doses of hydrochlorothiazide associated with clinically significant diuresis have been associated with impaired milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Inzirqo and any potential adverse effects on the breastfed infant from Inzirqo or from the underlying maternal condition.

Data

A single study involving one woman and her infant showed a peak concentration of 275 mcg/L at 3 hours following 50 mg dose. No drug was detected (<20 mcg/L) in the infant's plasma at 2 and 11 hours following the mother's dose.

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/s/

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