Cross-Discipline Team Leader and Division Summary Review

Date	1/22/2025
From	Doanh Tran
Subject	Cross-Discipline Team Leader and Division Summary Review
NDA/BLA # and Supplement#	NDA 219141
Applicant	Novitium Pharma LLC
Date of Submission	3/28/2024
PDUFA Goal Date	1/28/2025
Proprietary Name	Inzirqo
Established or Proper Name	Hydrochlorothiazide
Dosage Form(s)	Powder for oral suspension, 10 mg/mL
Applicant Proposed Indication(s)/Population(s)	• 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) • Treatment of edema (b) (4) (b) (4) including nephrotic syndrome, (b) (4) (b) (4)
Applicant Proposed Dosing Regimen(s)	(b) (4) (b) (4) *For* (b) (4) *of hypertension:* The (b) (4) initial dose is 25 mg daily 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) (b) (4) *For edema in adults:* The (b) (4) dose is 25 mg to 100 mg daily in single or divided doses. (b) (4) (b) (4) intermittent therapy (e.g., on alternate days or 3 to 5 days per week) (b) (4) (b) (4) electrolyte imbalance. (b) (4) *hypertension):* The (b) (4) pediatric dosage is 1 to 2 mg/kg per day in sin 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. (b) (4) less than 6 months of age, doses up to

	3 mg/kg per day in two divided doses may be required.
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	• INZIRQO is indicated for the treatment of hypertension in adult and pediatric patients, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions. • Treatment of edema associated with congestive heart failure, hepatic cirrhosis, and renal disease including the nephrotic syndrome in adult and pediatric patients.
Recommended Dosing Regimen(s) (if applicable)	See "Applicant Proposed Dosing Regimen(s)." Minor modifications made to language to reflect current labeling practices.

Material Reviewed/Consulted	
Integrated Quality Review (1/13/2025)	Stephanie Springer, Zhengfu Wang, Charudharshini Srinivasan, Lixia Cai, Alexander Gontcharov, Min Sung Suh, Haritha Mandula, Xia Xu, Nandini Bhattacharya, Grafton Adams, Theodore Carver
Pharmacology-Toxicology Review	Not applicable.
Clinical Pharmacology Review (1/21/2025)	Harisudhan Thanukrishnan, Doanh Tran
Clinical Review (1/21/2025, included as part of the Clinical Pharmacology Review)	Evan Fisher, Rekha Kambhampati
Office of Prescription Drug Promotion Reviews (1/16/2025)	Charuni Shah
Division of Medication Error Prevention and Analysis (DMEPA) Review (11/26/2024, 12/27/2024, 1/14/2025)	Jody Kundreskas, Nicole Iverson, Hina Mehta
Division of Pediatrics and Maternal Health Labeling Review (11/8/2024)	Kristie Baisden, Tamara Johnson

1. Introduction

On March 28, 2024, the Applicant, Novitium Pharma LLC, submitted NDA 219141 for Inzirqo (hydrochlorothiazide [HCTZ]) powder for oral suspension (PFOS) using the 505(b)(2) regulatory pathway. The Applicant is seeking the same indications as the listed drug (LD) Hydrodiuril tablets (NDA 011835). The application primarily relies on the Agency's previous finding of

safety and effectiveness for Hydrodiuril. As Hydrodiuril is discontinued, the Applicant conducted a pivotal relative bioavailability and food effect study (Study HTDR-21-047) comparing the 100 mg dose of their PFOS product to the designated Reference Standard (RS) HCTZ 100 mg tablets (50 mg x 2, Teva, ANDA 83177).

Overall, following a single dose of 100 mg, the extent of absorption (AUC) for HCTZ was comparable between HCTZ PFOS and the RS HCTZ tablets. The peak plasma concentration of HCTZ (C_{max}) for HCTZ PFOS was approximately 19% higher in the fasted state and 16% lower in the fed state, respectively, when compared with the RS HCTZ tablets. The RS HCTZ tablets can be taken with or without food and, based on these results, the review teams recommends that labeling indicate that HCTZ PFOS can also be taken with or without food. We concur with the review team and recommend approval of Inzirqo powder for oral suspension

2. Background

HCTZ tablets are approved for the treatment of edema, as an adjunctive therapy in edema, and for management of hypertension as the sole agent or to enhance effectiveness of other antihypertensives in the more severe forms of hypertension.

The Applicant's proposed product is a different dosage form (i.e., PFOS) compared to the LD (oral tablet). The Applicant claims that the PFOS dosage form may be preferred by patients with difficulty in swallowing (such as pediatric or geriatric populations) and will deliver an equivalent dose of HCTZ. The Applicant proposes to use the same dosing regimen as in the prescribing information for the LD.

3. Product Quality

The Integrated Quality Review from the Office of Pharmaceutical Quality recommends approval. Their summary review states the following.

Drug Substance: The drug substance reviewer noted that NDA 219141 references DMF (b) (4) for drug substance HCTZ. The DMF was found to be adequate to support this NDA. A Letter of Authorization dated October 15, 2024 was provided in the NDA.

Drug Product: The proposed drug product HCTZ PFOS is considered a non-sterile solid dosage form. All the excipients (except for the flavoring agents) are compendial and conform to USP/NF acceptance criteria and are found to be acceptable. The specification, batch analysis data, and stability data were determined to be acceptable after the Applicant responded to information requests related to testing, including reconstitution times, and agreed to reduce the time required for suspension based on the data provided in the application. As part of the risk assessment for (b) (4) impurities, the Applicant provided results from three exhibit batches at 6 months accelerated and as well as 24 months long term condition to demonstrate that (b) (4) (b) (4) levels were below the detection limit, which was less than (b) (4) % of the daily acceptable intake limit. Therefore, no additional controls for (b) (4) imp ies were required. A 24-month shelf life is acceptable based on the accelerated and long-term

stability data provided for three primary batches of the drug product. The in-use storage period for the liquid product after suspension is supported by the in-use stability studies provided.

Manufacturing: *Process* – The manufacturing process includes (b) (4) (b) (4) The proposed process controls and in-process controls are established based on development and registration batch results and were determined to be acceptable to support product quality. *Facilities* – All facilities were determined to be acceptable based on compliance status and inspection history.

Biopharmaceutics: The biopharmaceutics review primarily concerned the proposed dissolution method for the drug product. The Applicant accepted the agency's recommendations and revised the dissolution method, release and stability specifications, accordingly. The review team recommends approval for this NDA.

Microbiology: The microbiology review concluded that the supporting studies and specification, after revisions to the post approval stability protocol, support the proposed in-use storage period of 30 days after suspension. The review team recommends approval for this NDA.

Quality Labeling: The labeling was determined to be adequate from the quality perspective after the Applicant revised the labeling.

4. Nonclinical Pharmacology/Toxicology

Not applicable. A Nonclinical Pharmacology/Toxicology review was not needed for this NDA.

5. Clinical Pharmacology

The Office of Clinical Pharmacology recommends approval of NDA 219141. The NDA is primarily supported by the relative bioavailability study HYDR-21-047, a single dose cross-over study to compare the relative oral bioavailability (BA) and the effect of food on both the PFOS and the reference HCTZ tablets. As Hydrodiuril was discontinued and no longer available, the Applicant used the 50 mg HCTZ tablets of Teva Pharmaceuticals (ANDA 83177, the designated RS) for this study. In addition to this main study, the Applicant also conducted a pilot relative bioavailability study HYDR-20-115 for a preliminary assessment of the relative BA between the PFOS and the RS.

The results of study HYDR-21-047 showed that following administration of 100 mg under fasted condition, the AUCs for both products were similar (the Test/Reference geometric mean ratios (GMR) and 90% confidence intervals (CI) for AUC_{last} and AUC_{inf} were 1.03 (0.99-1.07) and 1.02 (0.98-1.06), respectively). The PFOS showed a higher C_{max} than the RS tablets and the GMR for C_{max} after administration in fasted state was 1.19 (1.10-1.28). Following a dose of 100 mg under fed condition, the 90% confidence intervals and the geometric mean ratio of PFOS product to reference HCTZ tablets were within the pre-specified bioequivalence limits of 80% to 125% for the ln-transformed AUC_{0-t} and AUC_{inf}, but not for the C_{max}. The C_{max} for the PFOS product was ~16% lower (90% CI 0.78 – 0.91). The review team agreed with the Applicant's

rationale that the approximately 19% higher C_{max} and the 16% lower C_{max} for PFOS in the fasted and fed state, respectively, are not expected to impact the clinical safety or efficacy of HCTZ for treatment of hypertension or edema.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

As discussed under Clinical Pharmacology, the relative bioavailability assessment provides the bridge to the efficacy findings of the LD, Hydrodiuril.

8. Safety

This application primarity relies on the Agency's previous finding of safety for the LD, Hydrodiuril (NDA 011835, Merck) and the RS (HCTZ tablets, ANDA 83177, Teva Pharmaceuticals). Although there was a slightly higher C_{max} for the proposed PFOS compared to the HCTZ tablets, there were no clinically significant differences observed between the PFOS and HCTZ tablets in supine or standing systolic or diastolic blood pressures, adverse events, serum electrolytes and 24-hour continuous urinary electrolyte excretion and the clinical reviewer did not have any safety concerns.

9. Advisory Committee Meeting

The application does not raise significant issues regarding the safety or effectiveness of the drug; hence, no Advisory Committee Meeting was held or needed.

10. Pediatrics

The Applicant did not conduct pediatric studies; they instead rely on the indications, dosing instructions, and other safety and efficacy information for the reference LD/RS. The prescribing information for the RS includes information on pediatric use under Precautions, as well as Dosage and Administration information for infants and children for the diuresis and control of hypertension. This information will be included in the Applicant's prescribing information, which has been updated to the Pregnancy and Lactation Labeling Rule (PLLR) format.

11. Other Relevant Regulatory Issues

None.

12. Labeling

The Office of Prescription Drug Promotion (OPDP) and the Division of Pediatrics and Maternal Health (DPMH) reviewed and provided comments on the proposed product labeling. The Division of Medication Error Prevention and Analysis 2 (DMEPA 2) reviewed and provided comments on carton and container labeling. Their comments were considered during final labeling revisions. DMEPA 2 also determined that the proposed proprietary name, Inzirqo, is acceptable.

13. Postmarketing Recommendations

None.

14. Recommended Comments to the Applicant

None.

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/

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01/24/2025 02:14:26 PM

ALIZA M THOMPSON
01/24/2025 02:37:52 PM
I concur.