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RESEARCH**

APPLICATION NUMBER:

220149Orig1s000

PRODUCT QUALITY REVIEW(S)



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Template Revision: 03

NDA Executive Summary

- Application/Product Information

NDA Number	220149
Applicant Name	Janssen Biotech, Inc.
Drug Product Name	ICOTYDE® (icotrokinra) Tablets, 200 mg
Dosage Form	Tablet
Proposed Strength(s)	200 mg
NDA Classification	Type 1 - NME
Route of Administration	Oral
Maximum Daily Dose	200 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy.
Drug Product Description	Janssen Biotech, Inc. submitted a new NDA220149 for ICOTYDE® (icotrokinra) Tablets, 200 mg via 505 (b)(1) regulatory pathway with a Rare Pediatric Disease Priority Review Voucher for the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy. This NDA is based on the IND 156446. The drug substance (DS), icotrokinra hydrochloride is a peptide consisting of 13 amino acids which is classified as a Biopharmaceutics Classification System (BCS) class 4 compound. It is a white to almost white powder with a decomposition temperature of 240 oC. It shows high aqueous solubility at acidic condition and low solubility between pH 5 and pH 9. The compound is

	consistently isolated as the non-stoichiometric crystalline HCl salt, (b) (4). The drug substance is hygroscopic and adsorbs water up to a level of ~9% change in mass at 80% RH. The drug substance is packaged in (b) (4). (b) (4). (b) (4). A retest period of (b) (4) months is proposed for the drug substance packaged in the commercial container closure system and stored at (b) (4) °C. Icotrokinra hydrochloride is formulated as a yellowish orange to yellowish brown, immediate release, oval shaped, film-coated tablet with a strength of 200 mg based on its free base. The drug substance is (b) (4). (b) (4). Icotrokinra Tablets, 200 mg is packaged in HDPE bottles of 30 tablets, with child-resistant (b) (4) closure with induction seal liner (b) (4) and silica gel desiccant (b) (4). A blister package with 7 tablets consists of an Aluminum (Alu) (b) (4) foil and an Alu lidding foil for sample use. The applicant provided up to 12 months long-term stability data at 25°C/60%RH and 6 months accelerated data at 40°C/75%RH for three primary registration batches (Batch#PCL4D, PCL4E and PCL4F) for the commercial package configuration. The proposed expiry period for the drug product is 24 months when stored at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted between 15 °C to 30 °C (59 °F to 86 °F) [see USP Controlled Room Temperature]. Store in original package to protect from moisture. Do not discard desiccant. Keep out of reach of children.
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Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	at 20°C to 25°C (68°F to 77°F) and excursions permitted to 15°C to 30°C (59°F to 86°F).		
Review Team	Discipline	Primary	Secondary
	Drug Substance	Sophie Rubashkin, PhD	Lawrence Perez, PhD
	Drug Product	Austin Yu, PhD	Baoqing Ma, PhD
	Manufacturing	Md Abdullah Mahmud, PhD	Zhaoyang Meng, PhD
	Biopharm	Kamrun Nahar, PhD	Tapash Ghosh, PhD
	Environmental Assessment	Xiaoqin Wu, PhD	James Laurensen, PhD
	Other (specify) Labeling	Austin Yu, PhD	Julia Pinto, PhD
	RBPM	Emma Gimose	
	ATL	Baoqing Ma, PhD	
Consults	N/A		

2. Final Overall Recommendation - Approval

This application is recommended for approval with the expiration dating periods of 24 months when packaged in the proposed container closure and stored at 20-25 °C.

The CMC-recommended PI labeling as well as container and carton labels revisions have been communicated to the applicant. The applicant has accepted all CMC-recommended revision and will submit the finalized PI labeling as well as container and carton labels to the application prior to the action date. Therefore, no additional labeling memorandum is needed for the approval of this application from the OPQ perspective.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

- The applicant of this 505(b)(1) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, Icotrokinra, and drug product, Icotrokinra tablets
- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC revisions on labels/labeling have been communicated to the applicant and the recommended CMC revisions have been accepted by the applicant.
- The applicant submitted an environmental assessment (EA) evaluating the potential environmental effects from the use of this drug product. The agency determines that approval of this application is not expected to have significant effects on the quality of the human environment. Therefore, the agency is issuing a finding of no significant impact (FONSI), and thus an environmental impact statement will not be prepared, per 21 CFR 25.15(b), 25.40, and 25.41

Therefore, from the OPQ perspective this application is recommended for approval with an expiration dating period of 24 months when stored at 20-25 °C.

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

Recommendation by Subdiscipline:

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

Environmental Assessment: Review & FONSI - Adequate

QPA for EA(s): Yes

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments:

Additional Lifecycle Comments: None

Application Technical Lead Name and Date:

Baoqing Ma, PhD
Senior Pharmaceutical Quality Assessor
DPQA VII/OPQA II/OPQ

01/12/2026

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CHAPTER III: ENVIRONMENTAL

R REGIONAL INFORMATION

1. Summary

Janssen Research & Development, LLC, the Applicant, submitted an environmental assessment (EA) for an original New Drug Application (NDA-220149-ORIG-1) regarding a drug product containing icotrokinra hydrochloride (icotrokinra; 200 mg Tablet), which is proposed for the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy. The estimated screening level expected introduction concentration (EIC) of icotrokinra in the aquatic environment is (b) (4) ppb, exceeding the categorical exclusion level of 1 ppb. Therefore, this application does not qualify for categorical exclusion from an EA, per 21 CFR 25.31(b), and the Applicant submitted an EA to evaluate the potential environmental effects from the use of this drug product.

FDA conducted a thorough review and assessment of the original EA and considered the original EA inadequate mainly due to the insufficient data on environmental fate of icotrokinra and its chronic toxicity to aquatic organisms. In response to an FDA information request (IR), the Applicant submitted additional information including two chronic toxicity tests of icotrokinra for daphnia and fish, a discussion on environmental persistence of icotrokinra, and an updated ecological risk assessment. The Agency concurs with the majority of the submitted data and analyses.

In conclusion, FDA has determined that the submitted information is sufficient to enable the Agency to determine whether approval of this drug application may significantly affect the quality of the human environment. Therefore, the EA is adequate for approval, per 21 CFR 25.15(a). Based on the submitted information, FDA has concluded that approval of this application is not expected to have significant effects on the quality of the human environment, and an environmental impact statement will not be prepared. A Finding of No Significant Impact (FONSI) is recommended for this application, per 21 CFR 25.15(b), 25.40, and 25.41.

2. Substance of Interest

The Applicant identified the active pharmaceutical ingredient (API) of the drug product, icotrokinra ($C_{90}H_{120}N_{20}O_{22}S_2$, molecular weight 1898.17 g/mol as free base), as the sole substance of interest for this EA. Icotrokinra, a 13-amino acid cyclic peptide, is a first-in-class oral peptide that selectively binds to the interleukin-23 receptor (IL-23R) with high

affinity and potency to competitively antagonize the binding of IL-23, resulting in inhibition of proximal IL-23R signaling and downstream effector functions. No information on excipients was provided in this EA.

3. Expected Introduction Concentration (EIC) of Icotrokinra

The Applicant estimated a peak production of icotrokinra in the next 5 years (2025-2030) of approximately (b) (4) kg/year in the U.S. market, based on which they calculated the EIC of icotrokinra in the aquatic environment to be (b) (4) ppb following the FDA 1998 guidance [1]. The Applicant also estimated an expected environmental concentration (EEC) of (b) (4) ppb by considering a dilution factor of 10 in receiving water.

The Applicant did not apply any depletion mechanisms, such as human metabolism/excretion or drug removal during wastewater treatment process, for the EIC refinement. According to the submitted information, icotrokinra is excreted predominantly in feces, with 37-81% of administered icotrokinra in feces as the unchanged parent compound and 0.0002-0.0007% in urine. No metabolites were detected in urine.

4. Physicochemical Property and Environmental Fate of Icotrokinra

The Applicant submitted physicochemical data of icotrokinra as summarized in the table below.

Physicochemical Parameter	Method	Results
Water solubility	OECD 105 (20 °C)	648 mg/L (pH 5); 43.1 mg/L (pH 7); 46.1 mg/L (pH 9)
Dissociation constant (pK _a)	OECD 112	5.88-6.0
Octanol-water distribution coefficient (logD _{ow})	OECD 107	-2.2 (pH 5, 7, 9)
Organic carbon-water partition Freundlich coefficient (K _{FOC})	OECD 106	Sludge: 274-278 L/kg Soil: 4,058-38,467 L/kg

The physicochemical data suggest that icotrokinra has a low potential for sorbing to the sludge in wastewater treatment plant (WWTP). Icotrokinra will most likely be confined to the aquatic compartment with negligible dispersion in sludge to the terrestrial environment. It is not expected to be volatile based on its molecular weight and melting point and thus will not enter the air compartment. Icotrokinra will enter the aquatic environment through effluents discharged by publicly owned treatment works. Based on this consideration, the evaluation of environmental effects of icotrokinra was limited to the aquatic environment. The physicochemical property of icotrokinra also suggests that it is not likely to bioconcentrate or bioaccumulate in fish.

The Applicant submitted environmental fate data of icotrokinra as shown in the table below.

Environ. Fate Study	Method	Results
Aerobic biodegradability	OECD 301F (28 days)	6-8% biodegradation; not readily biodegradable

The OECD 301F test results suggest that icotrokinra is not readily biodegradable under stringent test conditions. The Applicant provided a further discussion in their IR responses on the potential of icotrokinra for environmental persistence. They stated that the OECD 301F test results do not necessarily mean that icotrokinra is not biodegradable since the test only measured CO₂ as an endpoint and icotrokinra was not extensively degraded to CO₂ within the test period. The peptide structure of icotrokinra suggests that it will likely undergo enzymatic proteolysis by microorganisms in the environment, resulting in a mixture of small amino acids. Overall, although the degradation of icotrokinra in the environment has not been demonstrated, the Applicant considered that icotrokinra will likely biodegrade at least slowly over time, rather than being environmental persistent as would be the case for persistent pollutants such as polychlorinated biphenyls (PCBs) and dichlorodiphenyltrichloroethane (DDT).

5. Environmental Effects

The Applicant provided ecotoxicity data of icotrokinra on microbes in sewage sludge and aquatic organisms (algae, invertebrate, and fish) in freshwater. Results including no observed effect concentration (NOEC), the lowest observed effect concentration (LOEC), and various effect concentrations are summarized in the table below.

Organism	Method	Duration	Endpoint	Results
Microbes in activated sludge	OECD 209	3 hr	Respiration inhibition	NOEC ≥ 1,000 ppm
Green algae (<i>R. subcapitata</i>)	OECD 201	72 hr	Yield and growth rate	NOEC ≥ 100 ppm
Invertebrate (<i>D. magna</i>)	OECD 202	48 hr	Immobilization	NOEC ≥ 100 ppm
Invertebrate (<i>D. magna</i>)	OECD 211	21 d	Survival, reproduction, and growth	NOEC = 0.56 ppm LOEC = 1.5 ppm EC ₁₀ = 6.8 ppm EC ₅₀ > 13 ppm
Fish (<i>C. carpio</i>)	OECD 203	96 hr	Mortality and sublethal effects	NOEC ≥ 63 ppm
Fish (<i>P. promelas</i>)	OECD 210	32 d	Hatching success, post-hatch survival, growth (length and weight)	NOEC = 0.89 ppm LOEC = 3.0 ppm EC ₁₀ = 2.1 ppm EC ₅₀ > 11 ppm

Icotrokinra showed no effects on microbes in activated sludge and green algae at the highest test concentrations. It didn't show acute toxicity to daphnia and fish, but exhibited chronic effects on these organisms when exposure for a long period. The ecotoxicity data showed that icotrokinra inhibited the reproduction in daphnia with a LOEC of 1.5 ppm, and

caused a reduction in body weight in the early life stages of fish with a LOEC of 3.0 ppm. No other chronic effects were observed. Based on the submitted data, the lowest NOEC of icotrokinra for aquatic organisms is 0.56 ppm.

6. Environmental Risk Assessment

To assess the environmental risk of icotrokinra, the Applicant calculated the assessment factor (AF) as the ratio of the effect concentration to the environmental concentration (i.e., LC_{50}/EIC or EC_{50}/EIC ; or $NOEC/EEC$). The calculated AFs range from (b) (4) which are greater than the required factors (10-1000) in the FDA 1998 guidance [1], and in no case were sublethal effects at concentrations equal to the maximum EEC. Accordingly, the Applicant concluded that the release of icotrokinra to sewage treatment plants and the aquatic environment does not result in significant adverse environmental impact.

Assessment: Adequate

Environmental Review:

The main goals of this environmental review, per 21 CFR 25.15(a) and (b), and 25.40, are to determine (1) whether the EA contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment; and (2) if so, whether the proposed action will significantly affect the environment. Regarding the main findings of the submitted EA for NDA-220149-ORIG-1:

- The Applicant identified the API icotrokinra as the sole substance of interest for this EA. This is appropriate according to the FDA 1998 guidance [1], which notes that the EA should focus on the active moiety and the predominant structurally related substances expected to enter or exist in the environment.
- The EIC of icotrokinra in the aquatic environment ((b) (4) ppb) is acceptable. Icotrokinra is mostly excreted as the parent compound. Based on its physicochemical and environmental fate data, the WWTP removal rate of icotrokinra is expected to be low as icotrokinra is not readily biodegradable and unlikely to be removed through binding to the sludge. Therefore, it is reasonable that no refinement approach was applied for EIC reduction. As to the EEC, FDA considers that the standard dilution factor of 10 in the FDA 1998 guidance [1] has become less applicable as water scarcity and water reuse increases, and thus the EIC of (b) (4) ppb should be used for further ecological risk assessment.

- The submitted physicochemical and environmental fate data of icotrokinra are adequate. FDA agrees with the Applicant that only the water compartment needs assessment, as icotrokinra is not volatile and would not significantly partition to WWTP sludges. Once released to the aquatic environment, icotrokinra is expected to be mainly present in the water phase as it's highly water soluble and hydrophilic. Although no experimental data was provided to demonstrate that icotrokinra can be degraded to smaller molecules under realistic environmental conditions, FDA agrees with the Applicant that icotrokinra is likely to undergo microbial degradation in the environment based on its chemical structure. This biodegradation process, however, may be slow considering icotrokinra is a synthetic peptide with chemical modifications that may increase its environmental persistence compared to naturally occurring peptides. Regarding bioconcentration potential, FDA agrees that icotrokinra has low potential for bioaccumulation in fish and thus its risk to animals higher in the aquatic food chain is expected to be low.
- The submitted acute and chronic ecotoxicity data of icotrokinra are adequate. Icotrokinra didn't exhibit adverse effects on microbes in activated sludge and algae. Despite no acute toxicity was observed in daphnia and fish, icotrokinra showed chronic toxicity to these organisms when exposure was at ppm levels. The submitted data show that icotrokinra can inhibit the reproduction in daphnia and the growth in early life stage fish. FDA considers that the reproductive toxicity of icotrokinra to fish—which was assessed only to some extent, via OECD 210 (i.e., via a partial lifecycle test)—is expected to be low based on the mode of action of icotrokinra (selectively binding to the IL-23R) and its nonclinical toxicity data (no reproductive toxicity observed in rats).
- The approaches that the Applicant used for environmental risk assessments of icotrokinra in the aquatic environment generally adhere to the FDA 1998 guidance [1]. Based on the lowest NOEC of icotrokinra (0.56 ppm), FDA estimated the predicted no effect concentration (PNEC) of icotrokinra to be 56 ppb for the aquatic environment. FDA then calculated the risk quotient (RQ), i.e., the ratio of EIC to PNEC, to be 0.02, which is below the threshold value of 1. Therefore, FDA concludes that the adverse effects of icotrokinra on freshwater species, if there are any, are unlikely to be significant at the expected level of exposure.

Overall Assessment and Recommendation:

Overall, the submitted information for icotrokinra is sufficient to enable FDA to determine whether the proposed action may significantly affect the quality of the human environment. Therefore, the EA is adequate for approval.

Based on the information available to date, FDA has concluded that no significant environmental effects are expected from the approval of NDA-220149-ORIG-1. A Finding of No Significant Impact (FONSI) is recommended for this application.

References

1. U.S. FDA, 1998. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/environmental-assessment-human-drug-and-biologics-applications>

Primary Environmental Assessor Name and Date: *Xiaoqin Wu, 01/20/2026*

Secondary Assessor Name and Date: *James P. Laurenson, 01/22/2026*

Finding of No Significant Impact

NDA-220149-ORIG-1 Icotrokinra

200 mg Tablet, 200 mg Once Daily

Food and Drug Administration

Center for Drug Evaluation and Research

The National Environmental Policy Act of 1969 (NEPA) requires Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental effects of approving certain drug product applications and supplements to such applications as an integral part of its regulatory process.

Janssen Research & Development, LLC, the Applicant, is submitting an original New Drug Application (NDA-220149-ORIG-1) for the approval of icotrokinra for the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy. The active pharmaceutical ingredient, icotrokinra, is a first-in-class oral peptide that selectively binds to the interleukin-23 receptor (IL-23R) with high affinity and potency to competitively antagonize the binding of IL-23, resulting in inhibition of proximal IL-23R signaling and downstream effector functions.

In support of their application, the Applicant submitted an environmental assessment (EA) evaluating the potential environmental effects from the use of this drug product. The FDA Center for Drug Evaluation and Research (CDER) EA Team has reviewed and assessed the original EA and additional information submitted later in the Applicant's responses to an FDA information request (IR). The Agency has concluded that the submitted information is sufficient to determine whether approval of this drug application may significantly affect the quality of the human environment, and thus the EA is adequate for approval, per 21 CFR 25.15(a).

After consideration of potential adverse environmental effects due to approval of this drug application, FDA determines that approval of this application is not expected to have significant effects on the quality of the human environment. Therefore, FDA is issuing a finding of no significant impact (FONSI), and thus an environmental impact statement will not be prepared, per 21 CFR 25.15(b), 25.40, and 25.41.

Attachment: the original EA "Environmental Assessment for Icotrokinra (JNJ-77242113)" and the IR response letter

Janssen Research & Development, LLC

1.12.14 Environmental Assessment

ICOTROKINRA (JNJ-77242113)

Date	23 June 2025
Prepared by:	Janssen Research & Development, LLC
EDMS number	EDMS-RIM-1653038;v1.0

Confidentiality Statement

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Contents

1.	DATE.....	3
2.	NAME AND ADDRESS OF APPLICANT.....	3
3.	DESCRIPTION OF THE PROPOSED ACTION	3
3.1.	Requested Approval	3
3.2.	Need for Action	3
3.3.	Location of Use	3
3.4.	Disposal Sites	3
4.	IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION.....	3
4.1.	Nomenclature	4
4.2.	Chemical Abstract Service (CAS) Registry Number	4
4.3.	IUPAC Name	4
4.4.	Other names	4
4.5.	Molecular Formular.....	4
4.6.	Molecular Weight.....	4
4.7.	Structural Formula	5
5.	INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT	5
5.1.	Expected Introduction Concentration (EIC) from use of drug product	5
6.	ENVIRONMENTAL ISSUES	6
6.1.	Environmental Fate of released substances	6
6.2.	Environmental Effects (Tier 1 and Tier 2).....	6
6.3.	Summary of Environmental Fate/Effects	8
6.4.	Calculation of Assessment Factor	8
7.	MITIGATION MEASURES.....	9
8.	ALTERNATIVES TO THE PROPOSED ACTION.....	9
9.	PREPARER	9
10.	REFERENCES.....	10
11.	APPENDICES	11
11.1.	Appendix I (Confidential Information)	11
11.2.	Appendix II Preparer of EA (Non-Confidential Information)	12
12.	REFERENCES.....	13
13.	DATA SUMMARY TABLE	14

1. DATE

23 June 2025

2. NAME AND ADDRESS OF APPLICANT

Janssen Research & Development.
Turnhoutseweg 30
2340 Beerse
Belgium

3. DESCRIPTION OF THE PROPOSED ACTION

3.1. Requested Approval

Janssen Research & Development (JRD) is filing a New Drug Application (NDA) for Icotrokinra hydrochloride (JNJ-77242113-AAC) pursuant to Section 505(b) of the Federal Food, Drug and Cosmetics Act. Icotrokinra hydrochloride is a new molecular entity (NME) as it is not the active moiety in any drug product that has been approved by the FDA in any other application submitted under Section 505 of the Federal Food, Drug and Cosmetics Act. This environmental assessment (EA) pursuant to 21 CFR part 25 is prepared following the Centre for Drug Evaluation and Research “Guidance for Industry for Environmental Assessment of Human Drugs and Biologics Applications” (CDER 1998).

3.2. Need for Action

The product is intended for use for the treatment of moderate to severe plaque psoriasis in adult and pediatric patients 12 years of age and older who are candidates for phototherapy or systemic therapy.

3.3. Location of Use

The product will be dispensed by prescription and self-administered by patients at various locations in the US, including hospitals, clinics, and in private residences throughout the United States.

3.4. Disposal Sites

At US hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy, or clinic procedures. At home, empty or partially empty packages will typically be disposed by a community’s solid waste management system, which may include landfills, incineration, and recycling, although minimal of the unused product could be disposed of in the sewer system. Packaging materials for the therapeutic product will also enter the waste stream, these are widely available and used pharmaceutical packaging materials.

4. IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

Icotrokinra, also known as JNJ-77242113, is a first-in-class oral peptide that selectively binds to the IL-23R with high affinity and potency to competitively antagonize the binding of IL-23. This results in inhibition of proximal IL-23R signaling and downstream effector functions. After oral

administration of a single 10 mg dose, the amount of JNJ-77242113 excreted in urine could not be quantified because the concentrations were below the detection limit in all urine samples. In the multiple dose groups (10, 25, 100, 300 and 1000 mg), the amount of unchanged JNJ-77242113 excreted in urine over a 24-hour period as percentage of administered dose ranged from 0.0002 to 0.0007%. JNJ-77242113 measured in feces increased with dose, mean percentage unchanged JNJ-77242113 ranged from approximately 37% (10 mg once daily) to 81% (1000 mg once daily). Metabolite profiling in human plasma and urine showed that unchanged JNJ-77242113 was the major component in plasma. No circulating metabolites were detected, and no drug related material were detected in urine. As a consequence, the drug substance of interest entering the environment is JNJ-77242113 and is the focus of interest for this environmental assessment.

4.1. Nomenclature

4.1.1. Established name (USAN)

Icotrokinra hydrochloride

4.1.2. Brand/Proprietary Name/Trade Name

Not assigned

4.2. Chemical Abstract Service (CAS) Registry Number

304949-48-4 (Icotrokinra hydrochloride); 2763602-16-8 (Icotrokinra free base)

4.3. IUPAC Name

(4S)-4-([(4-[(2S)-2-[(2S)-2-[(4R,7S,10S,13S,16S,19R)-19-acetamido-7-(4-acetamidobutyl)-16-(2-amino-2-oxoethyl)-13-[(1R)-1-hydroxyethyl]-3,3,20,20-tetramethyl-10-[(7-methyl-1H-indol-3-yl)methyl]-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentaazacycloicosan-4-yl]carbonyl)amino]-3-[4-(2-aminoethoxy)phenyl]propanamido]-3-(2-naphthyl)propanamido]tetrahydro-2H-pyran-4-yl]carbonyl)amino]-5-[(2S)-4-amino-1-[(2S)-1-[(2-amino-2-oxoethyl)(methyl)amino]-1-oxo-3-(pyridin-3-yl)propan-2-yl]amino]-1,4-dioxobutan-2-yl]amino]-5-oxopentanoic acid hydrochloride

4.4. Other names

JNJ-2113, IL23Ri, Api2915, PN-21235, PN-235

4.5. Molecular Formula

C₉₀H₁₂₀N₂₀O₂₂S₂.xHCl (Icotrokinra hydrochloride, non-stoichiometric)

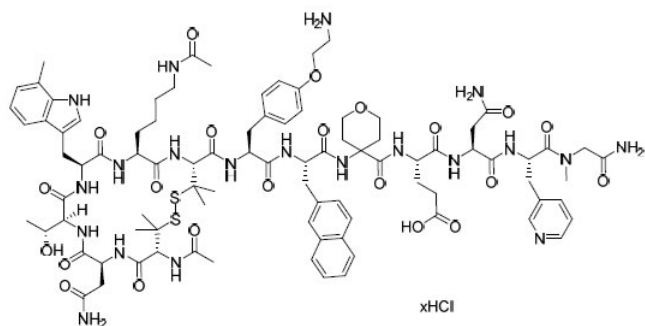
C₉₀H₁₂₀N₂₀O₂₂S₂ (Free base)

4.6. Molecular Weight

1898.17 + x36.46 g/mol (JNJ-77242113-AAC, Icotrokinra hydrochloride, non-stoichiometric)

1898.17 g/mol (JNJ-77242113, free base equivalent).

4.7. Structural Formula



5. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT.

5.1. Expected Introduction Concentration (EIC) from use of drug product

The fifth-year production estimate, the expected introduction concentration (EIC) and the expected environmental concentration (EEC) calculations for Icotrokinra are included in the Confidential Appendix ([Appendix 11.1](#)). The EIC in the aquatic environment is calculated using the following equation:

$$\text{EIC}_{\text{Aquatic}} (\text{ppb}) = A \times B \times C \times D$$

Where A = kg/year production (maximum in the next 5 years after introduction of the product)

B = 1/litres per day entering POTW ($1/1.2582 \times 10^{11} \text{ L/day}^a$)

C = year/365 days

D = $10^9 \mu\text{g/kg}$ (conversion factor)

For the calculation of the EIC it was assumed that:

- All quantities of the drug produced in a year are used and enter a publicly owned treatment works (POTW)
- Drug product usage occurs throughout the United States in proportion to the population and amount of wastewater generated.
- There is no metabolism of the active moiety
- There is no significant environmental depletion in the wastewater treatment process

Under these conservative assumptions, the EIC at the point of entry into the aquatic environment ($\text{EIC}_{\text{Aquatic}}$) was determined to be $> 1 \text{ ppb}$. Accordingly, the drug application is not categorically excluded, an environmental assessment (EA) is required.

a $1.2582 \times 10^{11} \text{ L/day}$ entering publicly owned treatment works (POTWs), Source: *2012 Needs Survey, Report to Congress*. Information regarding the *Needs Survey* is available on the Internet at <http://www.epa.gov/ovm>. It is updated periodically. $1.2582 \times 10^{11} \text{ L/day}$ is based on the 2012 information; 33,240 million gallons per day of wastewater entering POTWs multiplied by the conversion factor of 3.7853 L/gallon.

6. ENVIRONMENTAL ISSUES

6.1. Environmental Fate of released substances

6.1.1. Physical Chemical characterisation

Relevant data on physico-chemical properties are provided in the Data Summary Table ([Table 1](#)). The water solubility was determined following the OECD Guideline 105. The aqueous solubility at 20°C in aqueous buffers was determined to be 648 mg/L, 43.1 mg/L and 46.1 mg/L at pH 5, 7 and 9, respectively ([Study RMD 1403](#)). JNJ-77242113 is classified as negligible solubility (solubility < 0.1) according to EPA Classification System ([EPA 2012](#)).

The octanol/water distribution coefficient (D_{ow}), which expresses the concentration ratio of all species (neutral/ionic species) and may vary as a function of pH was determined at three pH values using the Shake-flask Method (OECD Guideline 107). At pH 5, 7 and 9, the log D_{ow} was determined to be -2.2, -2.2 and -2.2, respectively ([Study RMD 1403](#)). Based upon the log D_{ow} values obtained, JNJ-77242113 is not expected to significantly bioconcentrate in living organisms. The acid dissociation constant of JNJ-77242113 was determined by potentiometric titration following the OECD Guideline 112. Triplicate solutions of the test substance were titrated against standardized 0.01M aqueous hydroxide (NaOH) at $20 \pm 1^\circ\text{C}$. The pKa was calculated from the data generated on the pH, the volume of titrant added and the concentration of JNJ-77242113 and the concentration of the titrant. The mean pKa determined in the three experiments ranged from 5.88 to 6.0. The mean pKa was 6.0 (standard deviation 0.025) [[Study No. 20510078](#)].

JNJ-77242113 is not expected to be released to air or have a significant vapour pressure, based on its molecular weight and melting point (Henry's Law constant was not determined).

6.1.2. Environmental Depletion Mechanisms

An environmental biodegradation study was conducted with JNJ-77242113 according to OECD Guideline 301F (Manometric respiratory test). After an initial lag period of ca. 3 to 4 days during which microbial populations were likely getting acclimated to the test substance, biodegradation of JNJ-77242113 progressed slowly. The oxygen consumption in the test vessels after 28 days incubation revealed 6 and 8% biodegradation of the test substance dosed in the system. Therefore, the criterion for ready biodegradability (at least 60% biodegradation within a 10-day window) was not met JNJ-77242113 is considered not readily biodegradable. In the toxicity control, >25% biodegradation occurred within 14 days (48% based on ThOD). Therefore, JNJ-77242113 was considered not to inhibit microbial activity. In the procedural control (used to check the functioning of the test system), sodium benzoate was biodegraded by at least 60% (actual value 93%). All other validity criteria set in the OECD Guideline 301F (difference in replicate, total oxygen uptake in the blanks after 28 days, pH value in the test material vessels) were all within acceptable limits ([Study RMD 1400](#)).

6.2. Environmental Effects (Tier 1 and Tier 2)

Microbial Inhibition (Tier 1)

Microbial inhibition was evaluated by means of an activated sludge respiration inhibition test (ASRIT) according to OECD Guideline 209. The study was conducted as a combined limit/range finding test at three treatment levels (10, 100 and 1000 mg/L JNJ-77242113). Three replicates of the 1000 mg/L and one replicate each of the 10 and 100 mg/L treatment level, together with 6 replicates of an untreated control and four replicates of the reference substance 3,5-dichlorophenol were incubated over a period of 3-hours. The pH was measured, and the dissolved oxygen

consumption was monitored for over 10 minutes. From these measurements, the oxygen consumption rate was determined for each treatment level and control. No significant inhibition of the respiration rate observed at the 10 and 1000 mg/L treatment levels, and 11% inhibition was observed at the 100 mg/L treatment level. The effective concentration for 10% (EC₁₀) and 50% (EC₅₀) inhibition was determined to be >1000 mg/L. The No Observed Effect Concentration (NOEC) was determined to be 1000 mg/L ([Study RMD 1405](#)).

With no rapid depletion mechanism identified and a non-inhibitory effect on the respiration rate of activated sludge, JNJ-77242113 would be expected persist in the environment but not to disrupt wastewater treatment processes. According to the Tiered Approach to Fate and Effect testing, additional environmental effects testing was also conducted with algae, daphnia and Fish according to the OECD Guideline 201, OECD Guideline 202 and OECD Guideline 203, respectively to better understand the potential for adverse effects of JNJ-77242113 in the environment. Range finding and definitive tests were conducted with analysis of test substance concentrations during the test. All studies were conducted under GLP

Algal Toxicity (Tier Two)

The acute toxicity testing was conducted in Algae under static conditions following OECD Guideline 201. The study was conducted at nominal concentrations of 0.10, 1.0, 10 and 100 mg/L using the freshwater green alga *Raphidocelis subcapitata*. Six replicates of the highest concentration and three replicates each of the intermediate concentrations together with 6 replicates of the control were tested. To each replicate, approximately one million algal cells were added to 50 mL of algal growth medium in sterile 100 mL flasks to give an initial cell concentration of 10,000 cells/mL. The test vessels were orbitally shaken at 100 rpm for 72 hours. Light intensity throughout the study ranged between 400 to 700 nm. The temperature and pH during the test ranged from 22 to 24 °C and 7.6 to 8.1, respectively. At 24, 48 and 72 hours, a sample was removed from each flask for cell counting. These measurements were used to calculate the growth rate and biomass of each replicate. The results of the study were based on nominal concentrations of JNJ-77242113 and reported as the 72-hour EC₁₀, EC₂₀ and EC₅₀ values for biomass expressed as yield and average growth. The No-Observed-Effect Concentration (NOEC) values for total yield and average growth rate were also determined. The EC₁₀, EC₂₀ and EC₅₀ values for growth rate and yield were determined to be >100 mg/L based on the nominal concentrations of JNJ-77242113. The NOEC values for growth rate and yield were both ≥ 100 mg/L ([Study Number RMD 1406](#))

Invertebrate Acute Toxicity (Tier Two)

Acute toxicity testing was conducted in *Daphnia magna* under static conditions following OECD Guideline 202. The test was conducted as a combined limit/range finding test. Daphnids (<24 hours old) were exposed to JNJ-77242113 concentrations of 0 (control), 0.10, 1.0, 10 and 100 mg/L for 48 hours. Four replicate vessels of the highest concentration and control and two replicate vessels of the intermediate concentrations were prepared. Each of replicate vessels contained 5 daphnia in 50 mL treatment or control solution. Measured concentration in the top treatment at the start of the test was 102 mg/L, and during the 48-hour exposure was 97% of the nominal. The number of immobilized adults daphnids and observations of abnormal behavior were recorded daily. The temperature during the study was maintained at 20 to 21 °C and pH values ranged from 7.7 to 8.3 in all test and control solutions. Dissolved oxygen concentration remained above 66% saturation in all test solutions. No daphnid immobilization was observed after 48 hours in any of the test vessels. Therefore the 48-hour EC₅₀ based on mobility was determined to be >100 mg/L ([Study Number RMD 1407](#)).

Fish Acute Toxicity (Tier Two)

A fish acute toxicity test was conducted under static conditions according to OECD Guideline 203. Carp (*Cyprinus carpio*) were exposed under static conditions for 96 hours to nominal concentrations of JNJ-77242113 of 100 mg/L. Two replicate vessels were prepared: one for the test solutions and the other for the control, each vessel containing 7 fish. Dissolved oxygen concentrations, pH and temperature of the solutions were recorded. Fish were observed for mortality and signs of sublethal effects daily for the test period of four days. The measured concentration of JNJ-77242113 was significantly lower than the nominal dose level but remained stable at 112% relative to the initial during the test. The temperature of the test solutions averaged 21 °C, pH values ranged from 7.4 to 7.9 (test solutions) and 7.1 to 7.9 (control). Dissolved oxygen concentrations were 6.8 to 9.0 mg/L (test solutions) and 6.9 to 8.9 mg/L (control). No mortality or sublethal effects were observed during the four-day observation period. Therefore, the 96-hour LC₅₀ for JNJ-77242113 was greater than 63 mg/L, the geometric concentration tested. Based on the geometric mean measured concentrations, the 96-hour LC₅₀ value for *Cyprinus carpio* exposed to JNJ-77242113 was determined to be >63 mg/L ([Study Number RMD 1408](#)).

6.3. Summary of Environmental Fate/Effects

The expected introduction concentration (EIC) of Icotrokinra into the aquatic environment was calculated based on the fifth-year marketing estimate assuming all quantities produced are used and enter a POTW as active moiety. Under this conservative assumption the EIC exceeds 1 ppb at the point of entry into the aquatic environment. For estimation of the expected environmental concentration (EEC) it is assumed that no depletion mechanisms exist, and no dilution occurred in the receiving waters. Under these conservative assumptions, the maximum expected environmental concentration (MEEC) is considered to be equivalent to the EIC or EEC.

JNJ-77242113 will enter the aquatic environment through effluents discharged by publicly owned treatment works. Icotrokinra is not expected to be volatile and therefore will not enter the air compartment. Based on this consideration, the evaluation of environmental effects was limited to the aquatic environment. The octanol/water partition coefficient which indicates the tendency of a substance to accumulate in fatty tissue suggests that JNJ-77242113 would not be expected to bioconcentrate or bioaccumulate. The ecotoxicity of JNJ-77242113 to sewage treatment microorganisms and to three aquatic species was investigated using standard test protocols. The aquatic toxicity studies showed no indication of adverse effects at environmentally relevant concentrations. The ratio of the effect concentrations to the MEEC was greater than the Tier 1 and Tier 2 assessment factors, which indicated that there is no significant aquatic risk related to the environmental introduction of Icotrokinra.

6.4. Calculation of Assessment Factor

An assessment factor (AF) is calculated using the single species toxicity data and the exposure concentration (EIC/EEC). The calculations using the EIC assume no depletion mechanisms, while the calculations using the EEC assume depletion mechanisms and other losses (e.g. by adsorption or dilution).

$$AF = \frac{\text{Toxicity endpoint}}{\text{Environmental Concentration}}$$

The [CDER 1998 Guidance](#) lists three action levels based on the assessment factor obtained at various tiered levels of testing:

Test Tier	Assessment factor
Tier 1 – one suitable test organisms	1000
Tier 2 – Base set data	100
Tier 3 – Chronic toxicity testing	10

If the calculated AF is greater than the or equal to the AF for the different tiers, it can be concluded that no further action is required. The AF for JNJ-77242113 were calculated using the L(E)C50 from the acute studies (algae, daphnia and Fish) and the NOEC/EC10 where available (algae, ASRIT). A summary of the calculated assessment factors is presented below.

Toxicity test	L(E)C50	AF = L(E)C50/MEEC	Required AF
Sewage microorganisms (3 hours)	1000000	>977512	≥1000
Algae (72-hours)	EC ₅₀ >100000	97751	≥100
Daphnia (48-hours)	EC ₅₀ >100000	97751	≥100
Fish (96-hours)	EC ₅₀ = 63000	6361583	≥100

MEEC is the maximum expected concentration

In accordance with the CDER Guidance for Industry related to the Tiered approach to environmental effects testing, no further testing should be conducted if the median effective concentration (EC50) or the lethal concentration LC₅₀ divided by the maximum expected concentration is greater than or equal to 1000 for the test Tier 1, 100 for test Tier 2 or 10 test Tier 3 assessment factors. As the calculated assessment factors are significantly higher than the required assessment factors, it can be concluded that no significant adverse environmental impact is expected from the introduction of JNJ-77242113 residues into the environment.

7. MITIGATION MEASURES

Based on the data presented in this environmental assessment, no potential adverse environmental impacts are foreseen with the use or disposal of the product in the United States. Therefore, no mitigation measures are necessary.

8. ALTERNATIVES TO THE PROPOSED ACTION

No adverse environmental impacts have been identified at the expected introduction concentration. Therefore, no alternatives to the proposed action are needed.

9. PREPARER

Curriculum vitae, documenting the credentials of the preparer of this environmental assessment is provided in non-confidential appendix ([Appendix II](#)).

10. REFERENCES

Center for Drug Evaluation and Research (CDER), Center for Biologic Evaluation and Research (CBER). Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications. CMC 6. Revision 1. July. 1998.

21CFR25: Code of Federal Regulations Title 21 – Food and Drugs. Chapter I, Title 21 - Food and Drugs Administration, Department of Health and Human Services Subchapter A – General. Part 25 Environmental Impact considerations. Revised as of April 1, 2014.

Activated Sludge respiration Inhibition Test with JNJ-77242113-AAC. Test Facility Study No. 20510081. Sponsor reference No. RMD1405.

Determination of Ready Biodegradability (Manometric respirometry test) of JNJ-77242113-AAC with JNJ-77242113-AAC (OECD 301F). Test Facility Study No. 20510079. Sponsor reference No. RMD1400.

Freshwater Algal growth inhibition test with JNJ-77242113-AAC. Test Facility Study No. 20510085. Sponsor reference No. RMD1406.

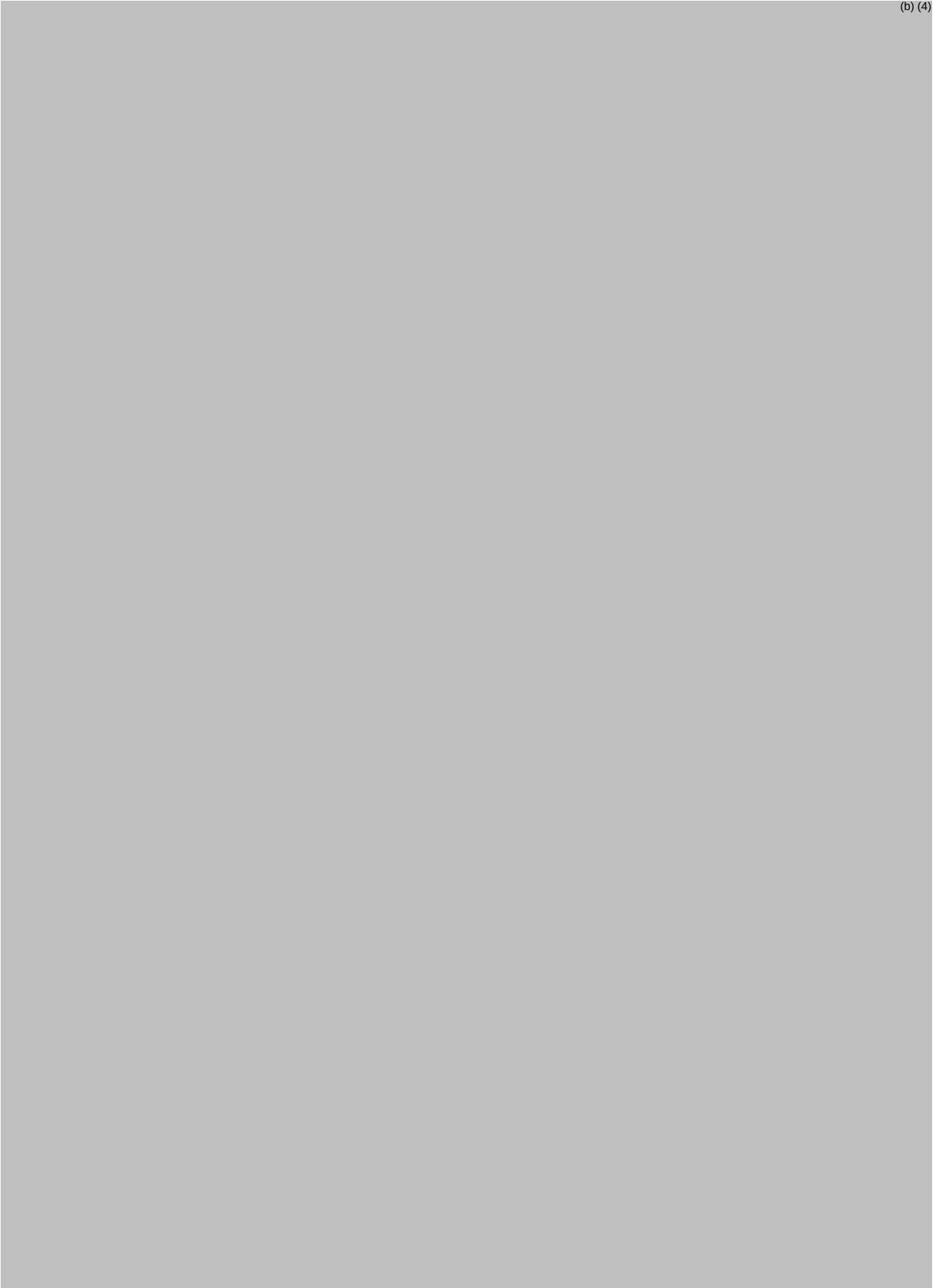
Daphnia magna, acute immobilization test with JNJ-77242113-AAC. Test Facility Study No. 20510086. Sponsor reference No. RMD1407.

Fish acute toxicity study with JNJ-77242113-AAC. Test Facility Study No. 20510087. Sponsor reference No. RMD1408.

11. APPENDICES

11.1. Appendix I (Confidential Information)

(b) (4)



11.2. Appendix II Preparer of EA (Non-Confidential Information)

Erick Nfon PhD, IBERA Certified Risk Assessor
Principal Environmental Risk Assessor Johnson & Johnson

Education

Ph.D. Applied Environmental Science
M. Eng. Chemistry/ MSc. Chemistry
BSc (Hons) Chemistry/Diploma Chemical Process Technology

Professional Memberships

SETAC (Society of Environmental Toxicology and Chemistry)
ACS (American Chemical Society)
Sveriges Ingenjörer (Swedish Association of Graduate Engineers).

12. REFERENCES

U. S. Department of Health and Human Services (DHHS), Food & Drug Administration (FDA), CBER). Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications. CMC 6. Revision 1. July 1998.

21CFR25: Code of Federal Regulations Title 21 – Food and Drugs. Chapter I, Title 21 - Food and Drugs Administration, Department of Health and Human Services Subchapter A – General. Part 25 Environmental Impact considerations. Revised as of April 1, 2014.

U.S. Environmental Protection Agency Office of Chemical Safety and Pollution Prevention EPA-748-B12-001. Sustainable Futures/P2 Framework Manual. EPA-748-B12-001 (2012).

Activated sludge respiration inhibition test with JNJ-772442113-AAC. Sponsor reference RMD 1405.

Freshwater Algal growth inhibition test with JNJ-77242113-ACC. Sponsor reference RMD 1406.

Daphnia magna acute immobilization test with JNJ-77242113-AAC. Sponsor reference RMD 1407.

Fish acute toxicity study with JNJ-77242113-AAC. Sponsor reference RMD 1408.

Determination of ready biodegradability: Manometric respirometry test of JNJ-77242113-AAC (OECD 301F). Sponsor reference 1400.

Determination of the dissociation constant of JNJ-77242113-AAC. Test Facility Study No. 20510078.

Determination of physico-chemical properties of JNJ-77242113-AAC. Partition coefficient at 3 pH values; water solubility at 3 pH values and Method validation. Sponsor reference RMD1403.

13. DATA SUMMARY TABLE

Table 1: Physical-chemical properties, environmental fate and effects data for JNJ-77242113.

PHYSICAL CHEMICAL CHARACTERIZATION	
Water Solubility	648 mg/L (pH 5); 43.1 (pH 7); 46.1 (pH 9)
Dissociation Constant (pKa)	pKa = 6.0
Partition Coefficient (log K _{ow} /log Dow)	log Dow = -2.2 (pH 5, 7 and 9)
Vapour pressure/Henry's Law Constant	--
Sorption Coefficient	--
DEPLETION MECHANISMS	
Aerobic Biodegradation	Not readily biodegradable (BOD/ThOD)
Hydrolysis	--
Photolysis	---
ENVIRONMENTAL EFFECTS	
Acute Toxicity	
Algae (OECD 201)	Green Alga 72-h EC ₅₀ > 1000 mg/L growth rate 72-h NOEC
Daphnia (OECD 202)	Water Flea (Daphnia magna) 48-h EC ₅₀ > 100 mg/L 48-h NOEC
Fish (OECD 203)	Carp (<i>Cyprinus carpio</i>) 96-h LC ₅₀ > 63 mg/L
Chronic toxicity	
Microbial Inhibition (OECD 209)	No inhibition up to 1000 mg/L EC ₅₀ > 1000 mg/L NOEC = 1000 mg/L

ATTACHMENTS

Attachment 1: JNJ-77242113 – Daphnia reproduction test

Attachment 2: JNJ-77242113 – Fish early-stage toxicity test (OECD 210)

Attachment 3: JNJ-77242113 – Adsorption in soils and sludges (OECD 106)

BIOPHARMACEUTICS REVIEW**NDA:** 220149**Drug Product Name / Strength:** Icotrokinra hydrochloride film-coated tablets, 200 mg**Route of Administration:** Oral**Applicant Name:** Janssen Research & Development**Indication:** Treatment of moderate to severe plaque psoriasis in adult and pediatric patients 12 years of age and older**Submission date:** 07/18/2025**Primary Reviewer:** Kamrun Nahar, Ph.D.**Secondary Reviewer:** Tapash Ghosh, Ph.D.**Recommendation:** Adequate**BACKGROUND:**

The Applicant is seeking approval under 505(b)(1) regulatory pathways for NDA 220149, Icotrokinra hydrochloride film-coated immediate release tablets, 200 mg, for the treatment of moderate to severe plaque psoriasis in adult and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy. This biopharmaceutics review evaluated the adequacy of information and data supporting: 1) the proposed dissolution method and acceptance criteria, 2) formulation bridging throughout product development, 3) effect of acid reducing agent on drug, and 4) compatibility of the water-dispersed tablets. The results are summarized below-

1) Dissolution Method and Acceptance Criteria: Adequate

Approved dissolution method and acceptance criterion for quality control and stability testing of the proposed product Icotrokinra hydrochloride film-coated tablets, 200 mg at release and stability:

Apparatus/ Vessel	Rotation Speed (rpm)	Medium	Volume (mL)/ Temperature	Dissolution acceptance criteria
USP apparatus 2 (paddle)/ Apex vessel	50	0.1M Citrate Buffer, pH 4.5	500/ 37.0°C±0.5°C	$Q = \frac{(b)}{(4)}\%$ in 15 minutes

2) Bridging of Formulations: Adequate

The Applicant conducted two pivotal bioavailability studies to successfully bridge formulations across clinical development phases. Study PSO1003 bridged the Phase 2 100 mg IR tablet to the Phase 1 oral solution. Study PSO1006 bridged the Phase 3 200 mg tablet to Phase 2 formulation (2×100 mg). Along with this in vivo study, dissolution testing confirmed similar release profiles (>85% at 15 minutes) for both formulations. The commercial formulation differs from pivotal clinical batches only by debossment markings

("200" and "JNJ"), which does not impact tablet quality, dissolution profiles between the pivotal phase 3 and commercial formulation showed similar drug release in the QC dissolution method.

3) Alcohol dose dumping: Not applicable

Since the proposed product is an immediate release oral (b) (4), alcohol dose dumping study is not required.

4) Biowaiver request: Not applicable

The proposed product has single strength with is used in pivotal phase 3 studies. Therefore, biowaiver request is not submitted.

5) Effect of acid reducing agent: Adequate

Icotrokinra exhibits pH-dependent solubility with low solubility at pH (b) (4), initially suggesting potential acid-reducing agent interactions per FDA guidance. However, dissolution testing revealed rapid drug release under (b) (4) conditions, though results varied with different pH 4.5 buffer systems - showing slower release with (b) (4) acetate buffer (<83% in 30 minutes) but rapid release with sodium citrate buffer. Additionally, biorelevant two-phase testing Fasted State Simulated Gastric Fluid (FaSSGF)→ Fasted State Simulated Intestinal Fluid (FaSSIF) demonstrated (b) (4) indicating no meaningful impact of acid-reducing agents on drug release.

6) Compatibility study: Adequate

The dissolution performance evaluation provided critical evidence supporting water dispersion compatibility. Comparative testing demonstrated that dispersed tablets in 240 mL of water exhibited dissolution profiles very similar to intact tablets, with both achieving rapid release (>85% dissolved within 15 minutes). The similar dissolution profiles confirm that water dispersion does not adversely affect drug release characteristics.

CONCLUSION AND RECOMMENDATION:

From a Biopharmaceutics perspective, NDA 220149 for Icotrokinra tablets, 200 mg is **adequate** for approval.

BIOPHARMACEUTICS ASSESSMENT:**Description and composition of the drug product:**

The 200 mg tablet contains Icotrokinra hydrochloride equivalent to 200 mg Icotrokinra free base. It is a yellowish orange to yellowish brown oval film-coated tablet (19 mm × 9 mm) debossed with "200" on one side and "JNJ" on the other.

Formulation development and bridging:

The Applicant conducted two pivotal bioavailability studies to bridge formulations used across clinical development phases. Study PSO1003 successfully bridged the Phase 2 100 mg immediate release tablet to the Phase 1 oral solution formulation. Study PSO1006 effectively bridged the Phase 3 200 mg tablet formulation to the Phase 2 100 mg tablet formulation (administered as 2×100 mg to achieve equivalent 200 mg dosing). The dissolution profiles of batches used in these studies showed similar release characteristics when tested with the proposed quality control dissolution method, with both Phase 2 and Phase 3 formulations achieving greater than 85% dissolution within 15 minutes.

The commercial formulation is identical in composition to the pivotal clinical batches used in Phase 3 studies, differing only by the addition of debossment markings ("200" on one side and "JNJ" on the other side) for product identification purposes. Comparative dissolution profiles between the pivotal phase 3 vs commercial formulations exhibits that debossing modification does not impact the tablet's dissolution performance by showing similar dissolution profiles.

Dissolution method development:

(b) (4)

(b) (4)

Discriminating ability:

The discriminating ability evaluation was conducted considering the critical material attributes, i.e., drug substance (DS) particle size distribution (PSD), critical formulations variables (CFVs), critical process parameters (CPPs).

Drug substance particle size distribution Evaluation:

The particle size discrimination study compared representative drug substance (dv10=(b) (4) μm, dv50=(b) (4) μm, dv90=(b) (4) μm) with (b) (4) (dv10=(b) (4) μm, dv50=(b) (4) μm, dv90=(b) (4) μm). (b) (4)

(b) (4)

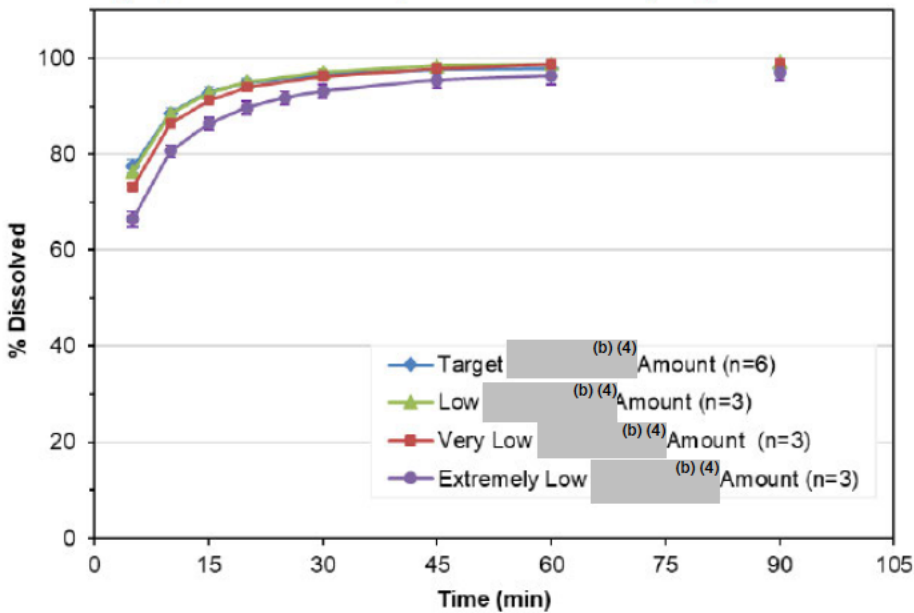
(b) (4)

(b) (4)

Critical formulation variables evaluation on discrimination:**(b) (4) Level Impact:**

Systematic evaluation of (b) (4) levels (target (b) (4) %, low (b) (4) %, very low (b) (4) %, extremely low (b) (4) %) revealed progressive discrimination patterns. While low and very low levels showed similar profiles to target, extremely low (b) (4) ((b) (4) %) demonstrated significantly slower dissolution with (b) (4) % differences for up to (b) (4) minutes.

Figure 14: Average dissolution profiles of drug product batches produced with different amount of (b) (4), using the proposed QC dissolution method, (n=3-6, ± SD)



(b) (4) **Assessment:**

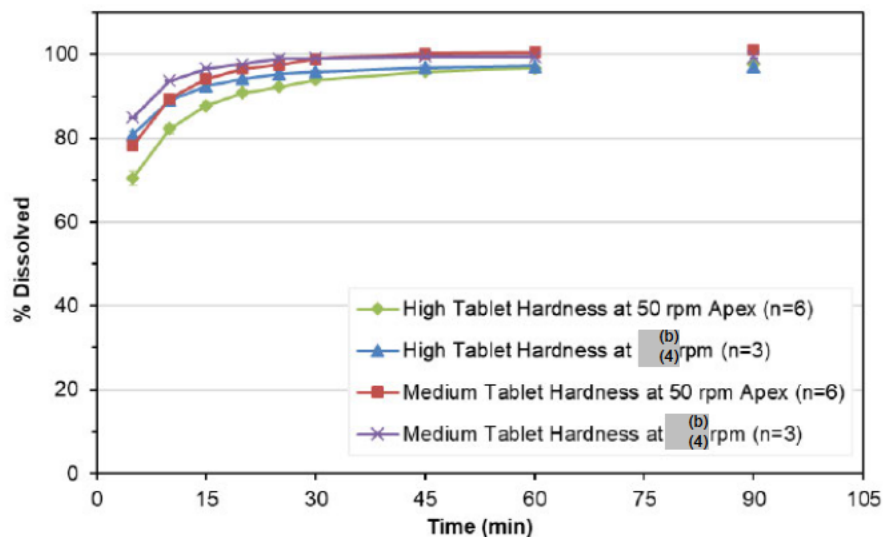
Testing of (b) (4) variations (target (b) (4)%, high (b) (4)%, very high (b) (4)%) showed no discrimination, with elevated (b) (4) levels producing similar dissolution profiles to target amounts.

Critical manufacturing process parameters on discrimination evaluation:

Tablet Hardness Sensitivity:

Evaluation of hardness variations (low (b) (4) N, target (b) (4) N, high (b) (4) N) showed significant discrimination for high hardness batches, with (b) (4)% differences maintained through (b) (4) minutes.

Figure 15: Average dissolution profiles of drug product batches produced with different tablet hardness values, using the proposed QC dissolution method, (n=3-6, $\pm$ SD)



Process Parameter Assessment:

(b) (4)

showed no discrimination capability, with dissolution profiles remaining similar across conditions.

Multivariate Sample:

The method successfully discriminated against a multivariate sample that combined multiple extreme variations ((b) (4) drug substance, high tablet hardness, low (b) (4) and high (b) (4)). The multivariate tablet showed significantly slower dissolution than the representative tablet, with differences exceeding (b) (4)% dissolved up to (b) (4) minutes and an f2-similarity factor <50 indicating dissolution profile differences between the target and aberrant formulations.

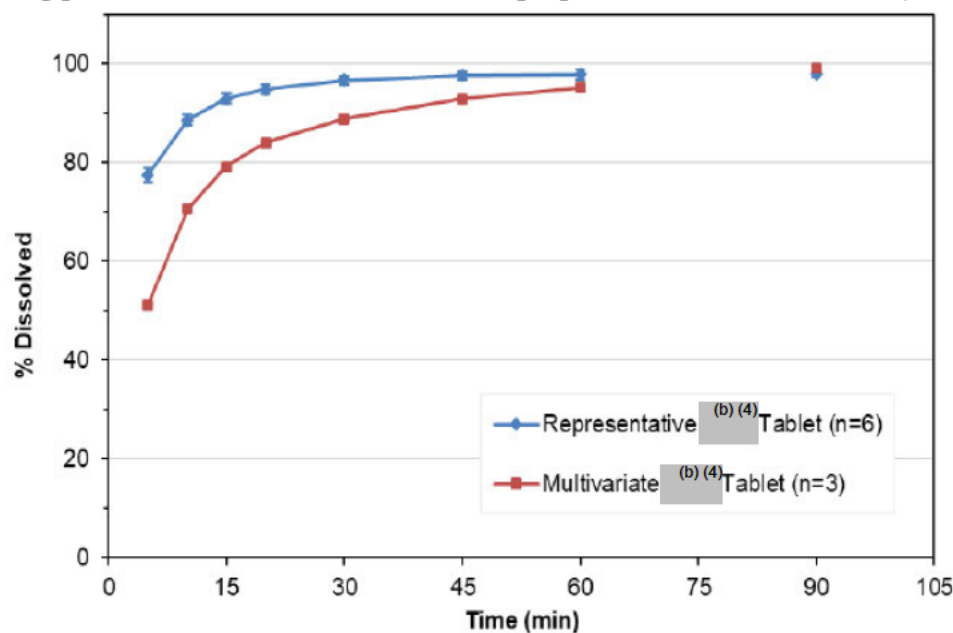
Table 5: Information on Drug Product Batches Used to Demonstrate Discriminating Capability for Multivariate Sample

Drug Product Batch	Drug Substance Batch	Label	Particle Size (µm) d _v 10 d _v 50 d _v 90	Tablet Hardness (N)	Amount of (b) (4)	Amount of (b) (4)
JNJ-77242113-n003-00421-132	A23BD0498	Representative				
JNJ-77242113-n003-01194-001	JNJ-77242113-n003-01196-002 ^a	Multivariate				

^a To obtain JNJ-77242113-n003-01196-002, drug substance batch A23FD1247 was (b) (4)

(b) (4)

Figure 16: Average dissolution profiles of the representative drug product batch and multivariate drug product batch, determined with the proposed dissolution method (± SD)



Stability Changes:

While stressed samples at 50°C/75% RH and 50°C/10% RH for 8 weeks showed similar profiles to unstressed material, this was expected given the drug product's chemical and physical stability.

In conclusion, the proposed dissolution method demonstrated suitable discriminating capabilities for quality control, (b) (4)

Dissolution method validation:

The dissolution method for Icotrokinra tablets, 200 mg, considering all required parameters including specificity, accuracy, precision, linearity, range, and robustness.

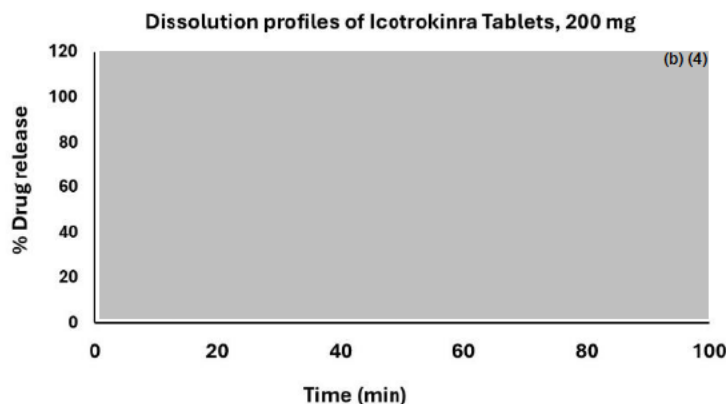
Robustness: Method remained valid across deliberate variations in analytical parameters (reference standard weight, mobile phase composition, flow rate, temperature) and dissolution parameters (paddle speed, temperature, buffer concentration, pH, volume, filter types).

Conclusion:

The dissolution method development for Icotrokinra successfully addressed BCS Class IV challenges through systematic optimization, identifying 0.10 M citrate buffer pH 4.5 and Apex vessels at 50 rpm as optimal parameters that eliminate coning artifacts while maintaining discrimination capability. The method demonstrates appropriate sensitivity to critical quality attributes ((b) (4), tablet hardness, multivariate changes). Based on the totality of the information, the dissolution method is deemed adequate.

Dissolution acceptance criterion:

The Applicant proposed the dissolution acceptance criteria as " $Q = \frac{(b) (4)}{(4)}\%$ in 15 minutes". Dissolution data showed (b) (4). Therefore, based on the dissolution data, the Applicant's proposed dissolution acceptance criterion is deemed adequate. Dissolution acceptance criterion is set as " $Q = \frac{(b) (4)}{(4)}\%$ in 15 minutes".



Approved dissolution method and acceptance criteria for the proposed Icotrokinra film coated immediate release tablets, 200 mg:

Apparatus / Vessel	Rotation Speed (rpm)	Medium	Volume (mL)/ Temperature	Dissolution acceptance criterion
USP Apparatus 2 (Paddle)/ Apex vessel	50	0.10 M Citrate Buffer, pH 4.5	500/ 37.0°C±0.5°C	Q = ^{(b) (4)} % in 15 minutes

Bridging among the formulations:

The development of Icotrokinra hydrochloride drug product evolved from early-stage oral solution formulations to a commercial immediate release film-coated tablet. Beginning with Phase 1 studies using Icotrokinra ^{(b) (4)} oral solutions ^{(b) (4)}

^{(b) (4)} and initial delayed release tablets ^{(b) (4)}

^{(b) (4)}, the program underwent a critical transition to ^{(b) (4)} form ^{(b) (4)}

Phase 2 development focused on immediate release formulations (25 mg G012 and 100 mg G014 tablets) that demonstrated superior pharmacokinetic consistency compared to delayed release alternatives, with bioequivalence studies confirming comparable performance between oral solution and tablet formulations. The Phase 3 program, ^{(b) (4)}, a 200 mg formulation (G078) ^{(b) (4)}

^{(b) (4)} were introduced. The final commercial formulation maintained the same qualitative and quantitative composition as clinical batches, with only the addition of debossing ("200" and "JNJ") for product identification, which was confirmed through dissolution studies to have no impact on performance.

^{(b) (4)}

Figure 17: Average dissolution profiles of plain Icotrokinra 200 mg film coated tablet (formulation G078), batch PCL4D, n = 12 and debossed 200 mg film coated tablet (formulation G078), batch PJJL7R, n = 6 using the proposed QC dissolution method ($\pm$ SD)

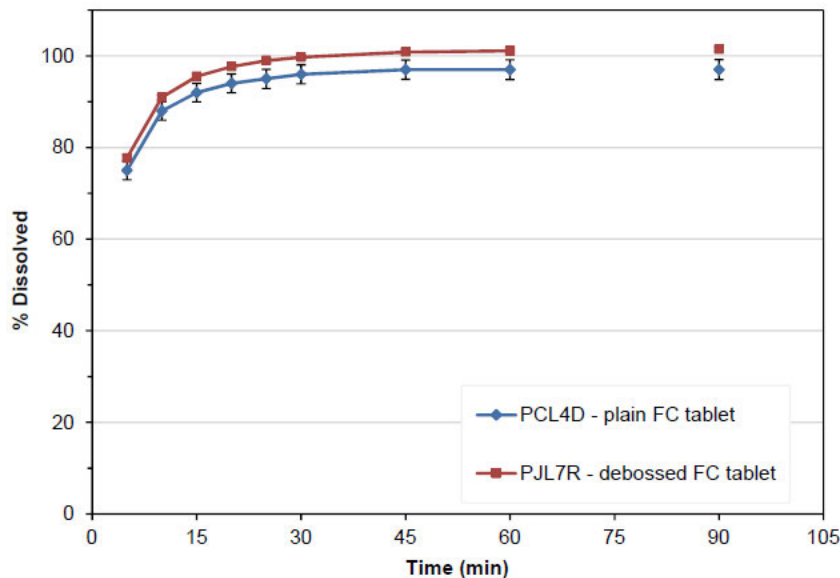
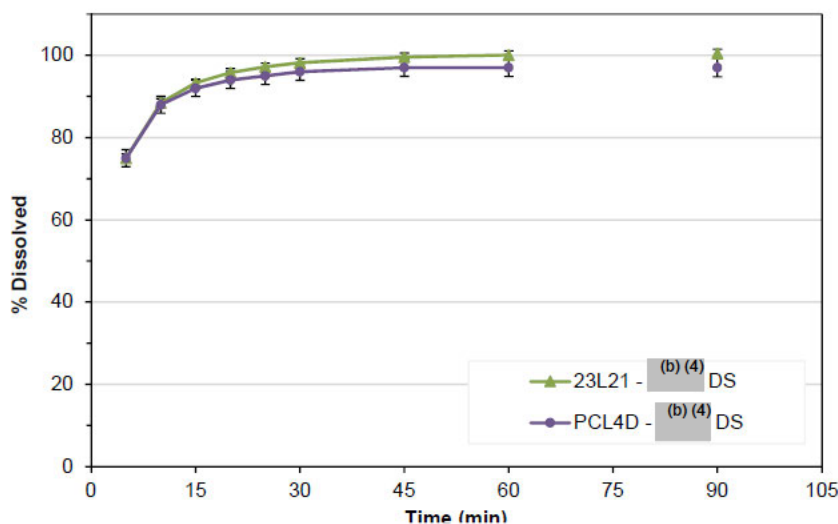


Figure 18: Average dissolution profiles of Icotrokinra 200 mg film coated tablet (formulation G078), containing (b) (4), batch 23L21, n = 6 and (b) (4), batch PCL4D, n = 12, drug substance using the proposed QC dissolution method ($\pm$ SD)



Effect of Acid Reducing Agents:

Icotrokinra exhibits pH-dependent solubility with low solubility at pH (b) (4) below the critical dose/250 mL threshold, initially suggesting potential acid-reducing agent interactions per FDA guidance: Evaluation of Gastric pH Dependent Drug Interactions with Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications Guidance for Industry (March

2023). However, dissolution testing at pH (b) (4) versus pH (b) (4) (b) (4)) showed very rapid drug release under both conditions. While standard dissolution testing confirmed pH-dependent behavior with rapid dissolution in (b) (4) and slower release at pH 4.5, (b) (4) buffer showed <83% drug release within 30 minutes, dissolution using the QC medium pH 4.5, 0.1M (b) (4) Citrate buffer showed very rapid drug release. Along with these data, biorelevant two-phase testing (FaSSGF→FaSSIF) demonstrated (b) (4)

Together all these data, thereby suggesting no meaningful impact of acid-reducing agents on drug release.

Figure 19: Average Dissolution Profiles of Drug Product Batch JNJ-77242113-n003-00205-004 Determined with a Paddle Apparatus at 50 rpm in Apex Vessels Using 500 mL of 0.1 M (b) (4) pH 4.5, (b) (4) at 37 °C (n=12, ± SD)

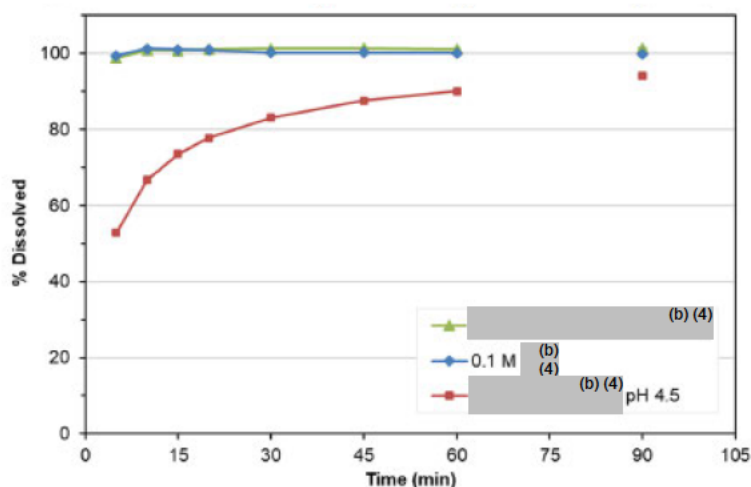
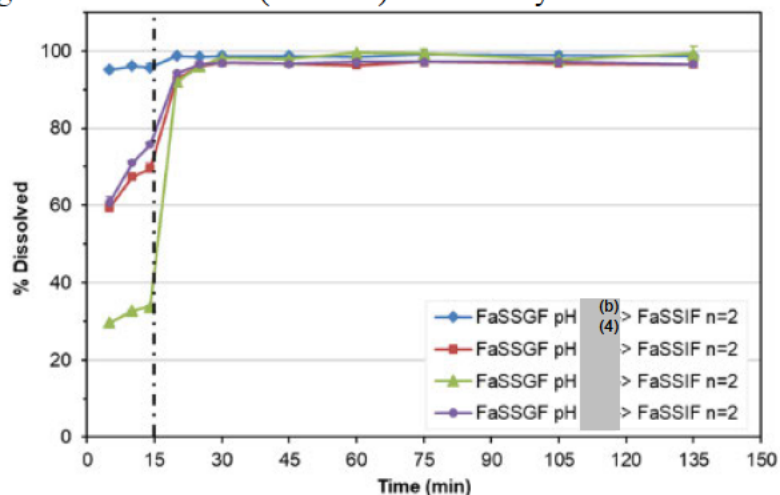


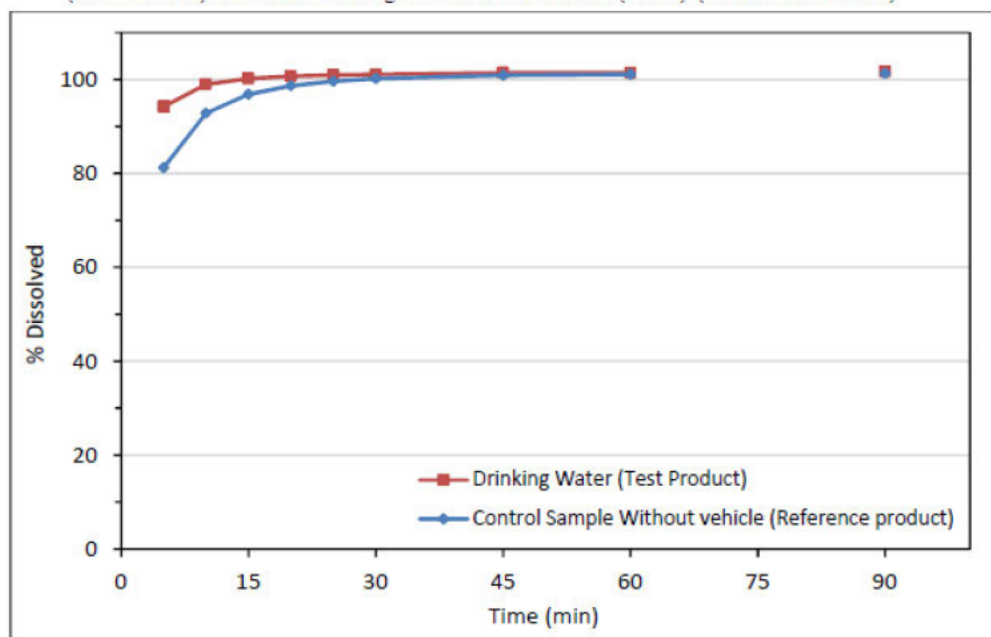
Figure 20: Dissolution profiles of Icotrokinra tablets, 200 mg with varying pH ranges in the gastric environment (FaSSGF) followed by the addition of intestinal media (FaSSIF, (b) (4))



6. Compatibility study:

The Applicant conducted comprehensive compatibility studies evaluating drinking water as an administration vehicle for the 200 mg film-coated tablet (G078), addressing immediate use and in-use stability scenarios. The study involved dispersing one tablet in 120 mL drinking water with 120 mL rinse, evaluated at initial, 1-hour, and 2-hour timepoints at room temperature (15-25°C), with analytical assessment of appearance, assay, chromatographic purity, and dissolution performance compared to intact tablet controls. Dissolution performance evaluation showed that water-dispersed tablets exhibited profiles very similar to intact tablets, with both achieving rapid release (>85% dissolved within 15 minutes) indicating that water dispersion does not adversely affect drug release characteristics.

Figure 21: Comparative dissolution profiles (n=12) of 200 mg film coated tablets G078 dispersed in drinking water (test product) vs intact 200 mg film coated tablets G078 (reference product)



Appendix 1. Dissolution Data

Dissolution data: <\\CDSESUB1\EVSPROD\nda220149\0011\m1\us\111-information-amendment\response-to-fda-ir-dated-15-oct-2025-nda-220149-cmc.pdf>



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Title:	NDA IQA Template CHAPTER IV-LABELING		
Document ID:	OPQ-ALL-TEM-0045		
Effective Date:	18 Sep 2023	Revision:	00
Total Pages:	24		



Template Revision: 03

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	220149
Assessment Cycle Number	1
Drug Product Name	ICOTYDE™ (icotrokinra) tablets

Assessment Recommendation: Choose an item.

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Inadequate	01
Patient Information	Inadequate	01
Instruction for Use (IFU)	Adequate	N/A
Container Labels	Inadequate	01
Carton Labeling	Inadequate	01

Brief Description of Outstanding Issues:

- Replace "TRADENAME" placeholder with the proprietary name (ICOTYDE).
- Include the street address with the city, state, and ZIP code.
- Include statement about child-resistant packaging.
- Provide an equivalency statement for the hydrochloride salt when appropriate.
- Include more physical attributes of the API.
- Specify whether the DP strength is based off the active moiety or salt in some sections.
- Include a statement to not consume the desiccant.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
eCTD 0001/SDN 01	2025 Jul 18	Prescribing Information Labeling, Patient Information, Instruction for Use, Container Labels, Carton Labeling.

1.0 PRESCRIBING INFORMATION¹

**Assessment of Product Quality Related Aspects of the Prescribing Information:
Inadequate.**

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Start Applicant Material

(b) (4)

End Applicant Material

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)

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 Highlights² [21 CFR 201.57(a)(2)]		
Established name(s) ³	Inadequate	Replace "TRADENAME" placeholder with the proprietary name.
Route(s) of administration	Adequate	Oral
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	[year] used by Applicant as a placeholder. This drug product has not been approved yet, so the year is pending.
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s) ⁴ and strength(s) in metric system ⁵	Adequate	The tablet is only available in one strength: 200 mg.
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	API is a salt, and the Applicant repeatedly states the strength based on the active moiety (200 mg of icotrokinra).
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: *Inadequate*

Replace "TRADENAME" placeholder with the proprietary name (ICOTYDE).

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>



Title:	NDA IQA Template CHAPTER IV-LABELING		
Document ID:	OPQ-ALL-TEM-0045		
Effective Date:	18 Sep 2023	Revision:	00
Total Pages:	24		



Template Revision: 03

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)⁹

Start Applicant Material

(b) (4)

End Applicant Material

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)

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).	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	Instructions detail that dosing should occur after waking up before the consumption of food. Instructions also mention avoiding crushing, splitting, or chewing the tablets.
For parenteral products: include statement: <i>"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."</i> 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).	N/A	
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 <i>"DRUG X is a hazardous drug. Follow</i>	N/A	

¹⁰ Draft Guidance: [Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments](#)

¹¹ §201.57(c)(3)(iv)

¹² USP General Notices 2.30 Legal Recognition

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
<i>applicable special handling and disposal procedures.^x</i> with x numerical citation to "OSHA Hazardous Drugs."		

Assessment: Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)¹³

Start Applicant Material

(b) (4)

End Applicant Material

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	One dosage form: tablet.
Strength(s) in metric system	Adequate	200 mg
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	In this section, the Applicant did not specify that the strength is based off the active moiety (icotrokinra).

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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	Yellowish orange to (b) (4) oval, film-coated tablets debossed with "200" on one side and "JNJ" on the other side.
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: *Inadequate*

Specify that the drug product strength is based off the active moiety (icotrokinra); a measurement of 200 mg was provided without an API.



Title:	NDA IQA Template CHAPTER IV-LABELING		
Document ID:	OPQ-ALL-TEM-0045		
Effective Date:	18 Sep 2023	Revision:	00
Total Pages:	24		



Template Revision: 03

1.2.3 Section 11 (DESCRIPTION)¹⁴

Start Applicant Material

(b) (4)

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

(b) (4)

End Applicant Material

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)].	Inadequate	Replace "TRADENAME" placeholder with the proprietary name.
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)].	Inadequate	The Applicant did not provide an equivalency statement for the hydrochloride salt.
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	

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)
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class ¹⁷ [§ 201.57(c)(12)(i)(E)].	Adequate	IL-23 receptor antagonist.
Chemical name ¹⁸ , structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	The chemical name, structural formula, and molecular weight are provided for the active moiety.
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Inadequate	The Applicant states that the solubility of the API hydrochloride salt is dependent on pH but does not specify an isoelectric point or ranges of maximum or minimum solubility.
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	Adequate	

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)
Drug Company X,” “structurally unique molecular entity”).		
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Assessment: *Inadequate*

Replace “TRADENAME” placeholder with the proprietary name (ICOTYDE), provide an equivalency statement for the hydrochloride salt, and specify an isoelectric point or ranges of maximum or minimum solubility because The Applicant states that the solubility of the API hydrochloride salt is dependent on pH.

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

Start Applicant Material

(b) (4)

End Applicant Material

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)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	Tablets.
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	One strength: 200 mg.
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	Bottles of 30 tablets.
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	Yellowish orange to yellowish brown, oval, film-coated tablets debossed with "200" on one side and "JNJ" on the other side.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	The tablet is not scored.
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures. ^x " with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	20 to 25°C, excursions permitted between 15 to 30°C.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free." ²¹	N/A	
Include information about child-resistant packaging ²² (if chosen by manufacturer).	Inadequate	No statement about child-resistant packaging were made in the labelling, but the application in P.7 mentioned a child-resistant cap. It is noted that the Applicant does include a statement to "keep out of reach of children" but this is not a declaration of child-resistant packaging.

²¹ Guidance: [Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex](#) (December 2014)

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

Assessment: Inadequate

No statement about child-resistant packaging were made in the labelling, but the application in P.7 mentioned a child-resistant cap.

1.2.5 Other Sections of Labeling

N/A

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.	Inadequate	The Applicant did not include a street address.

Assessment: Inadequate

The Applicant's address included the city, state, and ZIP code, but did not include the street.

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	Inadequate	Replace "TRADENAME" placeholder with the proprietary name.
Special preparation instructions (if applicable).	N/A	
Storage and handling information (if applicable).	Adequate	
If the product contains a desiccant, ensure the desiccant	Inadequate	The Applicant does not include a "do not eat" statement about the

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

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

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)
has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.		desiccant. The Applicant only included a statement to not discard the desiccant.
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.	Inadequate	The Applicant did not include a street address.

Assessment: *Inadequate*

The "TRADENAME" placeholder should be replaced with the proprietary name (ICOTYDE), a statement to not consume the desiccant should be present, and the street address should be included in the name and location of business.



Title:	NDA IQA Template CHAPTER IV-LABELING		
Document ID:	OPQ-ALL-TEM-0045		
Effective Date:	18 Sep 2023	Revision:	00
Total Pages:	24		



Template Revision: 03

3.0 CONTAINER AND CARTON LABELING²⁵

3.1 Container Labels²⁶

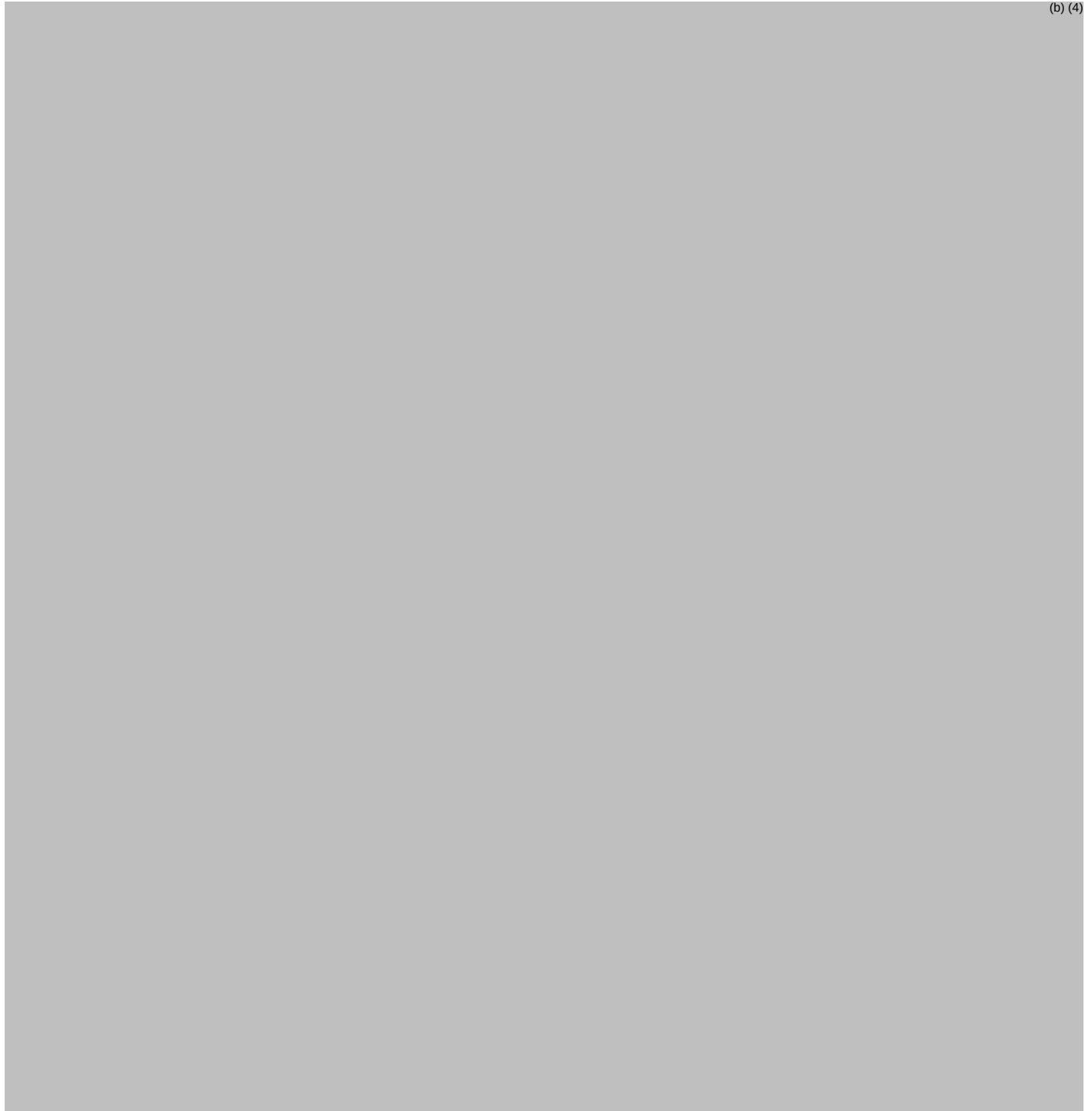
Container for bottle label:

(b) (4)

²⁵ [Carton and Container Labeling Resources](#)

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

Container for sample blisters label:



(b) (4)



Title:	NDA IQA Template CHAPTER IV-LABELING		
Document ID:	OPQ-ALL-TEM-0045		
Effective Date:	18 Sep 2023	Revision:	00
Total Pages:	24		



Template Revision: 03

3.2 Carton Labeling

Bottle label:



(b) (4)



Title:	NDA IQA Template CHAPTER IV-LABELING		
Document ID:	OPQ-ALL-TEM-0045		
Effective Date:	18 Sep 2023	Revision:	00
Total Pages:	24		



Template Revision: 03

Sample blisters label:



(b) (4)

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name ²⁷ , (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)]. ²⁸	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	Adequate	Yes	Active ingredient is the active moiety.
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)]. ²⁹	Adequate	Yes	Tablet count of 30 for the bottle. Sample blister packaging correctly indicates 7 tablets.
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	"Rx only" is displayed on all labels.
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	NDC is displayed on all labels.
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	Expiration in the format YYYY-MMM.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	No	Storage conditions displayed on all labels except the sample blister.

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

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

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

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).	N/A	Yes	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	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	No	Linear Bar code is present on all labeling except the sample blister.
Adequate directions for use: "Recommended Dosage: See	Adequate	No	Directions for use is present on all labeling except the sample blister.

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)
Prescribing Information" [§ 201.5 & 201.55].			
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	No	All labeling except the sample blister contain the phrase: "Manufactured for: Janssen Biotech, Inc."
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	No	"Keep out of reach of children" statement present in all labeling except the sample blister.
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Yes	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Yes	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Yes	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label. ³¹	N/A	Yes	
And others if space is available.	N/A	Yes	

³¹ USP General Notices 3.20 Indicating Conformance

Assessment of Carton Labels and Container Labeling: *Adequate*

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

- **Replace “TRADENAME” placeholder with the proprietary name (ICOTYDE) in the Patient Labeling and Prescribing Information Sections 11 and Highlights.**
- **Include the street address with the city, state, and ZIP code in the Patient Labeling and Prescribing Information Section Manufacturing Information.**
- **Include a statement about child-resistant packaging in the Prescribing Information Section 16.**
- **Provide an equivalency statement for the hydrochloride salt in Prescribing Information Section 11.**
- **Include more physical attributes (isoelectric point, solubility at different pH ranges) of the API in Prescribing Information Section 11.**
- **Specify whether the strength of the Drug Product is based off of the active moiety or hydrochloride salt in the Prescribing Information Section 3.**
- **Include a statement to NOT consume the desiccant in the Patient Labeling.**

Primary Labeling Assessor Name and Date:

AUSTIN YU (2025 DEC 16)

Secondary Assessor Name and Date (and Secondary Summary, as needed):

JULIA PINTO (2025 DEC 16)



Austin
Yu

Digitally signed by Austin Yu

Date: 12/16/2025 03:05:57PM

GUID: 65a1a6a80003545cc245d44de470837f



Julia
Pinto

Digitally signed by Julia Pinto

Date: 12/16/2025 03:45:41PM

GUID: 5050dbcb00001294a888a4bdc20a3a58