

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218347Orig1s000

OTHER REVIEW(S)



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Memorandum**

Date: April 19, 2024

Reviewer: Margie Goulding, PhD
Division of Epidemiology2 (DEPI-2)

Team Leader: Mingfeng Zhang, MD, PhD
DEPI-2

Director (Acting): Monique Falconer, MD, MS
DEPI-2

Subject: ARIA Sufficiency Memorandum

Drug Name(s): Upadacitinib (RINVOQ)

Application Type/Number: NDA 211675/S-21-22
NDA 218347

Applicant/sponsor: AbbVie

OSE TTT #: 2024-8797



EXECUTIVE SUMMARY

This memo present’s OSE’s ARIA Sufficiency Assessment for upadacitinib and the serious adverse events of (serious) infections, malignancies, thrombosis, and adverse growth effects in pediatric patients with polyarticular juvenile idiopathic arthritis (pJIA) or psoriatic arthritis (PsA). Due to limitations in measuring the incidence of these outcomes, particularly over the long term, and expected missing information on some important covariates, ARIA is not sufficient for evaluating these safety concerns with upadacitinib use.

Safety Concern	Serious infections	Malignancy	Thrombosis	Growth effects
Memorandum type				
-Initial				
-Interim				
-Final	X	X	X	X
Source of safety concern				
-Peri-approval	X	X	X	X
-Post-approval				
Is ARIA sufficient to help characterize the safety concern?				
-Yes				
-No	X	X	X	X
If “No”, please identify the area(s) of concern.				
-Surveillance or Study Population				
-Exposure				
-Outcome(s) of Interest	X	X	X	X
-Covariate(s) of Interest		X	X	
-Surveillance Design/Analytic Tools				

Abbreviations: AD = atopic dermatitis, PMR= post marketing requirement

1. BACKGROUND INFORMATION

1.1. Medical Product

Upadacitinib (Rinvoq) is an orally administered Janus kinase (JAK) inhibitor first approved 8/16/2019 as a 15 mg extended-release (ER) tablet for treating adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response (IA) or intolerance to methotrexate. Table 1 presents the current approved indications and dosages for Rinvoq ER.

Table 1. Rinvoq ER Indications and Dosage^a

Indication	Dosing
1.Adults with moderately to severely active rheumatoid arthritis (RA) who had inadequate response or intolerance to one or more TNF blockers (TNFi- IA).	15 mg once daily
2.Adults with active psoriatic arthritis (PsA) who are TNFi-IA.	15 mg once daily

^a U.S. Prescribing information for RINVOQ® (upadacitinib) extended-release tablets, for oral use, accessed at Drugs@FDA on April 9, 2024.



Table 1. Rinvoq ER indications and Dosage (cont'd)

Indication	Dosing
3. Adults and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis (AD) whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable.	Pediatric Patients 12+ Years of Age, Weighing at ≥ 40 kg and Adults < 65 Years of Age: Initiate with 15 mg orally once daily. If inadequate response, consider increasing to 30 mg once daily. • Adults 65+ Years: 15 mg daily • Severe Renal Impairment: 15 mg once daily
4. Adults with moderately to severely active ulcerative colitis (UC) who are TNFi-IA.	Induction dosage: 45 mg once daily for 8 weeks. Maintenance: 15 mg once daily or 30 mg once daily may be considered for patients with refractory/severe/extensive disease.
5. Adults with moderately to severely active Crohn's disease (CD) who are TNFi-IA.	Induction dosage: 45 mg once daily for 12 weeks. Maintenance: 15 mg once daily. A maintenance dosage of 30 mg once daily may be considered for patients with refractory, severe, or extensive disease.
6. Adults with active ankylosing spondylitis who are TNFi-IA.	15 mg once daily
7. Adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation who are TNFi-IA.	15 mg once daily

NDA 218347 seeks approval for a new formulation of upadacitinib, an oral solution for those unable to swallow solid forms. Also, NDA 211675 supplements 21 and 22 seek approval for adding indications for treating patients 2 - <18 years of age with pJIA or PsA. The proposed weight-based dosing for the new indications includes both solid and liquid formulations:

- 10 to <20 kg: 3 mg (3 mL oral solution) BID
- 20 to <30 kg: 4 mg (4 mL oral solution) BID
- 30 kg: 6 mg (6 mL oral solution) BID or 15 mg (one 15 mg ER tablet) QD.

The three applications are being reviewed together with an action goal date of 4/26/24.

1.2. Describe the Safety Concerns

The mechanism of action of upadacitinib, immunosuppression, and specifically suppression of multiple cytokine pathways within the immune system, carry the risks of **malignancy** and **serious/opportunistic infections**. Moreover, evidence from pre- and post-approval studies of upadacitinib and tofacitinib (another JAK inhibitor), respectively, in adult patients with rheumatoid arthritis (RA) were used to inform the post-market safety requirements for upadacitinib's new liquid formulation and pediatric indications (pJIA and PsA).

The US patient information (USPI) for RINVOQ includes this boxed warning (and the full warnings in Section 5):



**WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE
CARDIOVASCULAR EVENTS (MACE), and THROMBOSIS**

See full prescribing information for complete boxed warning.

- Increased risk of **serious bacterial, fungal, viral, and opportunistic infections** leading to hospitalization or death, including tuberculosis (TB). Interrupt treatment with RINVOQ ^(b)₍₄₎ if serious infection occurs until the infection is controlled. Test for latent TB before and during therapy; treat latent TB prior to use. Monitor all patients for active TB during treatment, even patients with initial negative, latent TB test.
- Higher rate of all-cause **mortality**, including sudden cardiovascular death with another Janus kinase (JAK) inhibitor vs. tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients.
- **Malignancies** have occurred in patients treated with upadacitinib. Higher rate of **lymphomas and lung cancers with another JAK inhibitor** vs. TNF blockers in RA patients.
- Higher rate of **MACE (defined as cardiovascular death, myocardial infarction, and stroke) with another JAK inhibitor** vs. TNF blockers in RA patients.
- **Thrombosis** has occurred in patients treated with upadacitinib. Increased incidence of pulmonary embolism, venous and arterial **thrombosis with another JAK inhibitor** vs. TNF blockers.

The supporting data on serious infections, thrombosis and malignancy come from the following sources:

1. From upadacitinib's ("UPA") clinical development program for RA, the 12/4/2019 clinical review's (REF ID 4528703) Section 8.9. Integrated Assessment of Safety reported:

On serious infections risk --

"A higher rate of serious infections was observed in a dose-dependent manner of UPA-treated subjects compared to control subjects across all analysis sets. Overall, there was a greater percentage of subjects experiencing a serious infection when treated with UPA 15 mg compared to PBO-treated subjects. This greater percentage of serious infections was dose-dependent with higher proportions of UPA 30 mg-treated subjects reporting serious infections compared to subjects treated with UPA 15 mg, PBO or MTX."

On malignancy risk –

"While these data suggest that there is no increased risk of malignancy with UPA, excluding NMSC, it should be noted that the data are limited due to the majority of subjects being exposed to UPA for one year or less. Prolonged immunosuppression is associated with an increased risk of malignancy, thus, there is the potential for an increased risk of malignancies with long-term (>1 year) UPA treatment consistent with safety signals from other immunosuppressant drugs and drugs from the JAK inhibitor class."

And on VTE risk –

"... adjudicated VTEs were reported at comparable rates in UPA-treated subjects and subjects treated with PBO, MTX and ADA. No dose-dependent relationship in the rates of VTE, patterns in the time to onset of the events, or association with platelet count were observed. The long-term incidence rates for UPA 15 mg were within the range of VTE rates reported for the general RA population. As stated with the malignancy analysis, these data need to be interpreted with caution due to the majority of subjects having been exposed for one-year or less. It is unclear whether an increase of VTEs may occur with longer term (>1 year) treatment with UPA in light of safety signals from other drugs in the JAK inhibitor class."



2. From tofacitinib’s (“TOFA”) PMR safety study in adult patients with RA:

Table 1: *Adverse events in treatment groups from the Phase 3b/4 Randomized Safety of a JAK inhibitor (tofacitinib) vs. a TNF Inhibitor (in Subjects with Rheumatoid Arthritis)*

Comparing treatment with another JAK inhibitor (Tofacitinib (TOFA)) 10 mg daily vs. inhibition of tumor necrosis factor-alpha (TNF)				
Endpoint (FDA Source Table)	Patients with event # (%)		RR	95% CI
	TNF (N=1451)	TOFA10 mg (N=1456)		
MACE	43 (3.0)	59 (4.1)	1.37	0.93-2.01
Malignancy except NMSC (ISS, T.14)	42 (2.9)	60 (4.1)	1.42	0.97-2.10
Lymphoma (ISS, T.15)	1 (0.1)	6 (0.4)	5.98	0.72-49.6
Death (ISS, T. 16)	38 (2.6)	66 (4.5)	1.73*	1.17-2.56
Thrombosis (ISS, T. 16)	56 (3.9)	86 (5.9)	1.53*	1.10-2.13
Comparing treatment with another JAK inhibitor (Tofacitinib (TOFA)) 5 mg daily vs. inhibition of tumor necrosis factor-alpha (TNF)				
Endpoint (FDA Source table)	Patients with event # (%)		RR	95% CI
	TNF (N=1451)	TOFA5 mg (N=1455)		
MACE (ISS, T. 14)	43 (3.0)	50 (3.4)	1.16	0.78-1.74
Malignancy except NMSC (ISS, T. 14)	42 (2.9)	62 (4.3)	1.47*	1.00-2.16
Lymphoma (ISS, T. 15)	1 (0.1)	4 (0.3)	3.99	0.45-35.6
Death (ISS, T. 16)	38 (2.6)	49 (3.4)	1.29	0.85-1.95
Thrombosis (ISS, T. 16)	56 (3.9)	67 (4.6)	1.19	0.84-1.69

SOURCE: ISS=Integrated Safety Review (8/16/2021 Ref ID: 4842642) results for tofacitinib Tables 14-16; Clinical Study Report Table 14.2.2.1; RRs and 95% CIs calculated by DEPI (Ref ID: 4919300).

Abbreviations: RR: relative risk; CI: confidence interval; MACE: Major Adverse Cardiovascular Event; NMSC: non-melanoma skin cancer

Note: Relative Risks marked with an * are significantly elevated. The lower bounds of the 95% CIs for these RR estimates are 1 or higher.

Growth Effects

In addition, adverse effects of upadacitinib on bone growth in pediatric patients is a concern stemming from animal study results. Juvenile rat studies of JAK inhibitors ruxolitinib and baricitinib showed adverse effects on bone growth and development (assessed by histopathology), including growth arrest, and reduced length and width of the femur and tibia. The examination of bone growth and development was incomplete for tofacitinib due to the juvenile animal studies lacking histopathology data for long bones and joints. A PMR observational study to evaluate potential effects on growth in pediatric (≥2 years) pJIA patients was also required for tofacitinib. In Rinvoq’s development program embryo-fetal development studies found skeletal malformations including misshapen humerus, radius and femur bones in the offspring of rats treated with upadacitinib and

sternum malformations in the offspring of rabbits treated with upadacitinib.

In sum, based on these various pieces of safety data, for approval of Rinvoq Supplements 21 and 22, DRTM proposes to issue a new PMR to study the long-term safety risks, including malignancy, infection, thrombosis and adverse growth effects in pediatric patients treated with upadacitinib.

Note: Approval of pJIA indication for **tofacitinib** has a PMR (#3944-1) to conduct a long-term observational study in pediatric patients 2-17 years of age with pJIA treated with tofacitinib to evaluate the risk of malignancies, serious infections, thrombosis and effects on growth. The trial completion month is planned for 02/2030.

1.3. Regulatory Purpose

Purpose	Safety Concern	Serious infection	Malignancy	Thrombosis	Adverse Growth Effects
Assess a known serious risk		X	X	X	
Assess signals of serious risk					
Identify unexpected serious risk when available data indicate potential for serious risk					X

1.4. Regulatory Objectives

To conduct a long-term observational study in pediatric patients to characterize both:

- a) the known risks of malignancy, serious infections, and thrombosis found in adult patients treated with upadacitinib or other JAK inhibitors, and
- b) the hypothesized risk of adverse effects on bone development suggested by animal studies.

This study should:

- define baseline risk factor profiles for patients who initiate upadacitinib and a comparator group initiating standard of care therapy,
- collect prospective data on the drug exposures and long-term safety outcomes with at least five years of follow-up for serious infections, malignancy, thrombosis and adverse effects on growth,
- adjudicate these outcomes and estimate their incidence over 5 years of follow-up.

Note: The 2019 approval of Rinvoq ER 15 mg tablets, for treating adults with RA triggered PREA (Pediatric Research Equity Act), a statutory requirement that the drug be studied in the pediatric “equivalent” of the disease. The approval required the sponsor to conduct these 2 pediatric studies:

- 3680-1: a multiple-dose PHARMACOKINETIC (PK) study in children from 2 to less than 18 years of age with juvenile idiopathic arthritis. Final report deadline Feb. 2021
- 3680-2: a RANDOMIZED withdrawal, double-blind, placebo-controlled study to evaluate the efficacy and safety of upadacitinib in children from 2 to less than 18 years of age with polyarticular-course JIA. Final report deadline Oct. 2026



After reviewing the results of the submitted PK study 3680-1¹, which reported no deaths overall and in the upadacitinib-treated group *no malignancy*, NMSC, GI perforation, renal dysfunction, active tuberculosis, or adjudicated major adverse cardiac events and venous thromboembolism, DRTM decided to release the sponsor from PMR 3680-2 (the randomized study), and instead proposes to issue a new PMR for an observational safety study to characterize the long-term safety risks in this pediatric patient population with at least five years of follow-up.

1.5. Effect Size of Interest or Estimated Sample Size Desired

Due to the low prevalence of the underlying diseases and very small, expected number of outcome events (other than infections), only a descriptive study with an active comparator group is being recommended. A formal statistical comparison of risk by exposure group (i.e. estimating a drug effect size, by testing a specified risk difference or relative risk) is not proposed. Also, while a registry is envisaged for the needed data collection (including growth (height) measures over time), and adjudication of the infection and thrombosis events, a minimum enrollment number (sample size) will not be specified.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

We defined the desired study population as pediatric patients 2- <18 years of age with a diagnosis of pJIA or PsA. pJIA is a subclass of a broader classification of juvenile idiopathic arthritis (JIA). pJIA can occur throughout childhood with onset from around 2 years onward. It is defined as arthritis with no other cause that affects five or more joints in the six months since onset (polyarticular). JIA has a yearly incidence of 2-20 cases/100,000 individuals with a prevalence of 16-150 cases/100,000 individuals¹. The total estimated number of pediatric patients in the US with JIA is 294,000². Among the seven subtypes of JIA, the pJIA subtype (see #2 & #3 in S.2.2 below) accounts for 13-35% of cases and the juvenile PsA subtype (#6 below) accounts for 2-11% of cases (Ravell, 2007).

2.2 Is ARIA sufficient to assess the intended population?

Yes. JIA is divided into seven subtypes with the icd-10 codes indicated:

- 1) oligoarticular JIA (M08.40),
- 2) seropositive polyarticular JIA (M05.9),
- 3) seronegative polyarticular JIA (M08.3),
- 4) systemic-onset JIA (sJIA) (M08.2),
- 5) enthesitis-related arthritis (ERA) (M08.80),
- 6) juvenile psoriatic arthritis (JPsA) ≈ psoriatic juvenile arthropathy (L40.54), and could be identified using the code for arthropathic psoriasis, unspecified (L40.50) combined with age

¹ The PK/safety study M15-340 is the study conducted for PMR 3680-1. It is also the body of safety data submitted to support Rinvoq for pJIA and peds PsA. The CSR was submitted on 3/24/23 to meet the submission deadline to provide PK data. The same CSR was re-submitted on 6/28/23 in S-021 for pJIA and cross-referenced in the submission of S-022 for peds PsA on 6/30/23.

This report is the one including PK and open-label, single arm safety data from 57 patients. The 120-day safety update submitted 10/15/23 includes safety data from an additional 26 patients, bringing the total to 83. Of these 83, 50 patients have available safety data up to at least 48 weeks.

The CSR and 120-day update are the “final” reports for the current submission. The Applicant uses the term “interim” to refer to the ongoing data collection of data from their enrolled patients. The plan is to collect up to 156 weeks if possible, but there are no milestones for the submission of that data. And the data are open-label with no comparator.

restrictions, and
7) undifferentiated JIA ≈ unspecified JRA ≈ juvenile arthritis (unspecified site M08.00/90, multiple sites M08.09).

3 EXPOSURES

3.1 Treatment Exposure

We defined the exposure of interest as a dispensing of Rinvoq ER tablets or the new oral solution.

3.2 Comparator Exposure

Standard of care agents, such as injections of etanercept (Enbrel and biosimilars), adalimumab (Humira and biosimilars) or abatacept (Orencia) have NDC codes that could be used to identify patients administered these alternative therapies for pJIA and PsA.

3.3 Is ARIA sufficient to identify the exposure of interest?

Yes. A National Drug Classification (NDC) code for upadacitinib 15 mg tablets (0074-2306) permits identification of patients with a dispensing for the tablet form of upadacitinib. We assume that an NDC code for the oral solution, which may become the more prevalent form used in the pediatric population, will become available with that form's approval.

4 OUTCOMES

4.1 Outcomes of Interest

- 1) **Malignancies** (probably excluding NMSC (non-melanoma skin cancer)). Malignancies initiated by drugs are expected to have a long latency period. DEPI defines malignancies as those first apparent 3 to 7 years after the first exposure to upadacitinib.
- 2) **Serious** (including opportunistic) **infections**. DEPI defines serious infections as infections that require hospitalization. A subset of serious infections are serious opportunistic infections, caused by pathogens to which immunosuppressed patients are especially vulnerable (pneumonia, GI infection, meningitis).
- 3) **Thrombosis** (including, DVT, PE, ATE...)
- 4) **Adverse effects on growth**, defined as changes in age-sex adjusted height measurements.

4.2 Is ARIA sufficient to assess the outcomes of interest?

NO. We assessed:

1. For malignancy, particularly those with a long latency period, we expect the average length of patients' participation in Sentinel's underlying health plans (around two years) will not allow long enough follow-up for full capture of this outcome. Also, verification of algorithms used to identify these outcomes in Sentinel would require confirmatory information from a linked cancer registry or primary review of the patient's medical record, which are not feasible currently in ARIA.
2. For growth measures, i.e., changes in age-sex-standardized height measures, periodic measures of height over time are needed. While height is technically available in ARIA (in the Sentinel Common Data Model), it is unlikely to be populated in a routine way that would allow for assessment of changes in growth.



3. In adults with RA, an algorithm for identifying VTE in US inpatient/ER and outpatient claims data had moderate validity (PPV=75.5%)³, but we could not find any validation studies in the pediatric population; and we expect that VTE events are rarer in the pediatric population.
4. In addition, for the regulatory purpose of signal evaluation, it is important that the safety outcomes of interest (serious infection, malignancy, and thrombosis) be identifiable with both high sensitivity and high specificity. Although a Sentinel study demonstrated high positive predictive value (PPV) for serious infections (as a group) in hospital data (80.2%), the sensitivity is unknown. Also, the PPVs for specific serious infections (gastrointestinal infection and meningitis) were only around 69%. Thus, certain types of serious infections in pediatric patients could be missed.

5 COVARIATES

5.1 Covariates of Interest

Age and sex are important baseline covariates to assess the child's growth. Also, any related hormonal deficiency would be important to know.

For malignancy, family history of malignancy is pertinent.

For serious infections, medical history such as HIV infection is relevant.

For thrombosis, underlying disease severity is a potential confounder (as in adults).

5.2 Is ARIA sufficient to assess the covariates of interest?

NO, not for all the covariates of interest. For patient's age and sex, ARIA's information is judged to be reliable and accurate. Although diagnosis coding in Sentinel claims may be reliable for identifying comorbidities and prior cancer, HIV infection or even a clotting pathology in the child before the drug exposure, the available look back period may not be long enough, and rheumatic disease severity measures and family disease history are generally unavailable.

For analysis of malignancy risk, it's important to have the information on prior cancer in the patient or their family, so ARIA is insufficient. For analysis of thrombosis risk, it's important to have a disease severity measure because of the link between arthritis severity, inflammation and thrombosis, so ARIA is insufficient.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

We assessed ARIA tools for safety surveillance: signal detection for growth effects and signal evaluation for serious infections, malignancy, and thrombosis outcomes.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes. ARIA's analytic tools are:
sufficient for:

- a) identifying upadacitinib uptake/initiation and use of comparator standard of care therapy,



- b) identifying patient's baseline demographic characteristics and comorbidities, and
- c) estimating the incidence of the outcomes and conducting inferential analysis.

7. NEXT STEPS

In a pre-signal assessment meeting (SAM) with representatives from the review division (DRTM), the OSE Sentinel Core Team and DEPI on April 5 and follow-up email communications (also including representatives from DPV and DRM), there was general agreement on the overall inadequacy of ARIA for the intended analysis, the need for primary data collection, outcomes adjudication and longer-term follow-up than ARIA allows. The childhood arthritis and rheumatology research alliance (CARRA) registry collects information allowing assessment of patterns of therapy and outcomes in pediatric patients with pJIA and PsA. It was recognized that conducting such a study outside of ARIA, potentially in CARRA, would still be challenging, but upon approval of NDA 211675 supplements 21 and 22, DRTM will issue a FDAA PMR for a study described as:

Conduct a long-term registry study in pediatric patients 2 to less than 18 years of age with polyarticular Juvenile Idiopathic Arthritis (pJIA) or Psoriatic Arthritis (PsA) treated with upadacitinib to characterize the risk of malignancies, serious infections (including opportunistic infections), thrombosis, and effects on growth. The registry should enroll upadacitinib-exposed patients and control groups of pediatric pJIA and PsA patients treated with standard-of-care. The sponsor should adjudicate the study outcomes. Patients should be followed for 5 years.

References

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet*. Mar 3 2007;369(9563):767-778. doi:10.1016/S0140-6736(07)60363-8
2. Espinosa M, Gottlieb BS. Juvenile idiopathic arthritis. *Pediatr Rev*. Jul 2012;33(7):303-13. doi:10.1542/pir.33-7-303
3. Kim S, Martin C, White J, et al. Validation of an Algorithm to Identify Venous Thromboembolism in Health Insurance Claims Data Among Patients with Rheumatoid Arthritis. *Clin Epidemiol*. 2023;15:671-682. doi:10.2147/CLEP.S402360

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/s/

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	April 17, 2024
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	NDA 218347
Product Name, Dosage Form, and Strength:	Rinvoq LQ ^a (upadacitinib) oral solution, 1 mg/mL
Applicant Name:	AbbVie, Inc.
FDA Received Date:	April 4, 2024
TTT ID #:	2023-5321-1
DMEPA 1 Safety Evaluator:	Neha Kumar, PharmD
DMEPA 1 Associate Director of Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES

^a The proposed proprietary name, Rinvoq LQ, was found conditionally acceptable by DMEPA on March 26, 2024 (PNR# 2024-1044725674).

1 PURPOSE OF MEMORANDUM

On April 4, 2024, the Applicant submitted revised container label, carton labeling, and instructions for use (IFU) for Rinvoq LQ. The Applicant implemented all our IFU recommendations, except for those stated in Section 2, in response to IFU recommendations that we made during a previous HF validation study results review.^b The Applicant also provided their rationale for not implementing the recommendations mentioned in section 2. We reviewed the revised IFU and rationale for not implementing certain recommendations to determine if they are acceptable from an HF perspective. In addition, we note that the Rinvoq LQ container label and carton labeling were found to be acceptable in a subsequent DMEPA label and labeling review.^c

2 CONCLUSION

The Applicant implemented all our recommendations, except:

- "Include instructions on inspecting the medication color in the "Preparing Rinvoq" section. For example, include these instructions with Step 2, "Check expiration date."

The Applicant states that instructions to inspect the color are not necessary. Although we stated in our review that per the Applicant's use-related risk analysis, if the user does not inspect the medication color there is risk of exposure to or administration of unknown substances^b, in their April 4, 2024 response, the Applicant clarifies that minor cosmetic color changes in drug product are not associated with this risk. The Applicant also states that *"The "Important Information" provided in the submitted IFU was implemented to provide information to the user of potential acceptable color variations in the solution. The upadactinib oral solution has been evaluated in ongoing stability studies and the results demonstrate that the appearance of the solution stays within specifications over 24 months. The solution remains clear, and the color remains within the proposed specification of 'colorless to light yellow'."*

- "Increase the prominence of the instructions, "Give the child a drink of water." by creating a separate step. Include an image corresponding with this step."

The Applicant states that *"The administration of water is a non-critical task and a lack of water administration to the child was assessed to only potentially cause negligible or minor (Severity 1 or 2) harms and therefore does not require the prominence of an additional step/figure or necessitate additional risk mitigation."* The Applicant also states that the drug product is only mildly acidic, roughly equivalent to cola or orange

^b Kumar, B. Human Factors Study Results Review for Rinvoq LQ (NDA 218347). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAR 21. TTT ID: 2023-5321.

^c Vee, S. Review of Revised Label and Labeling Memo for Rinvoq LQ (NDA 218347). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 APR 8. TTT ID: 2023-5320-2.

juice and the risk of the patient not drinking water is product residue left on sensitive mucosa or dentin. Thus, the Applicant determined that a separate step and corresponding image for the task, "Give the child a drink of water." is not necessary. However, the Applicant changed the statement "Give the child a drink of water." to appear as a new sub-bullet c within Step 12 "Give the oral solution", after "b. Push the plunger to give the entire dose in the child's mouth (see Figure L)". We find this change acceptable.

We find the Applicant's rationale to not implement the two recommendations acceptable. Based on the provided information, we have no additional recommendations for the revised Rinvoq LQ IFU at this time.

APPENDIX A. APPLICANT RESPONSE TO AGENCY LABELING RECOMMENDATIONS RECEIVED
ON APRIL 4, 2024

The Applicant's submission can be accessed in EDR via:

<\\CDSESUB1\EVSPROD\nda218347\0028\m1\us\111-information-amendment\label-response-narrativ-2024-mar-28.pdf>

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/s/

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: April 8, 2024
Requesting Office or Division: Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number: NDA 218347
Product Name, Dosage Form, and Strength: Rinvoq LQ (upadacitinib) oral solution, 1 mg/mL
Applicant/Sponsor Name: Abbvie
TTT ID #: 2023-5320-2
DMEPA 1 Safety Evaluator: Sarah K. Vee, PharmD
DMEPA 1 Team Leader (Acting): Damon Birkemeier, PharmD, FISMP, NREMT

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on April 4, 2024 for Rinvoq LQ (upadacitinib). The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container label and carton labeling for (upadacitinib) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Abbvie implemented all of our recommendations and we have no additional recommendations at this time.

^a Vee, S. Label and Labeling Review for (upadacitinib) (NDA 218347). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAR 12. TTT ID No.: 2023-5320-1.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SARAH K VEE
04/08/2024 10:35:05 AM

DAMON A BIRKEMEIER
04/08/2024 10:37:15 AM

HUMAN FACTORS STUDY REPORTS REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	March 21, 2024
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	NDA 218347
Product Type:	Combination Product (Drug-Device)
Product Name, Dosage Form, and Strength:	Upadacitinib ¹ oral solution, 1 mg/mL
Device Constituent:	Oral syringe and bottle
Rx or OTC:	Rx
Applicant/Sponsor Name:	AbbVie, Inc.
Submission Date:	June 28, 2023; December 4, 2023; March 12, 2024
TTT ID #:	2023-5321
DMEPA 1 Safety Evaluator:	Neha Kumar, PharmD
DMEPA 1 Associate Director for Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

¹ At the time of this review, the proprietary name was not approved. Thus, the established name, upadacitinib, is used in this review. However, we note that AbbVie submitted the proposed name Rinvoq LQ for DMEPA review on March 12, 2024.

1 REASON FOR REVIEW

This review evaluates the human factors (HF) study results reports submitted under NDA 218347 for upadacitinib oral solution.

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	Section/Appendix
Product Information/Prescribing Information	Section 1.1
Background Information Previous HF Reviews (DMEPA)	Section 1.2
Human Factors Study Reports	Appendix A
Information Requests Issued During the Review	Appendix B
Labels and Labeling	Appendix C
Detailed List of Use Errors, Use Difficulties, And Close Calls for Section 3.1	Appendix D

1.1 PRODUCT DESCRIPTION

Table 2. Relevant Product Information for Upadacitinib (oral solution (NDA 218347) and tablet (Rinvoq, NDA 211675) are listed in the same Prescribing Information)	
Initial Approval Date	• Tablet (Rinvoq): August 16, 2019 • Oral solution: pending approval
Active Ingredient	Upadacitinib
Indications	• Adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers • Adults with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers • Adults and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable • Adults with moderately to severely active ulcerative colitis who have had an inadequate response or intolerance to one or more TNF blockers • Adults with moderately to severely active Crohn's disease who have had an inadequate response or intolerance to one or more TNF blockers • Adults with active ankylosing spondylitis who have had an inadequate response or intolerance to one or more TNF blockers • Adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation who have had an inadequate response or intolerance to TNF blocker therapy • Proposed: ○ Pediatric patients 2 years of age and older with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers ○ Pediatric patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis who have had an inadequate response or intolerance to one or more TNF blockers
Route of Administration	Oral
Dosage Form	Tablet; proposed: solution
Strength	• Extended-release tablets: 15 mg, 30 mg, and 45 mg • Proposed: oral solution 180 mg/180 mL (1 mg/mL)
Dose and Frequency	<u>Adults with Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, and Non-radiographic Axial Spondyloarthritis</u>

- The recommended dosage of upadacitinib is 15 mg tablet once daily.

Atopic Dermatitis

- Pediatric patients 12 years of age and older weighing at Least 40 kg and adults less than 65 Years of age: Initiate treatment with upadacitinib 15 mg tablet orally once daily. If an adequate response is not achieved, consider increasing the dosage to 30 mg orally once daily.
- Adults 65 years of age and older: Recommended dosage of upadacitinib is 15 mg tablet once daily.
- Severe renal impairment: Recommended dosage of upadacitinib is 15 mg tablet once daily.

Ulcerative Colitis

- Adults: The recommended induction dosage of upadacitinib is 45 mg once daily for 8 weeks. The recommended maintenance dosage of upadacitinib is 15 mg tablet once daily. A maintenance dosage of 30 mg once daily may be considered for patients with refractory, severe, or extensive disease. Discontinue upadacitinib if adequate therapeutic response is not achieved with the 30 mg dosage. Use the lowest effective dosage needed to maintain response.
- See the Full Prescribing Information for the recommended dosage in patients with renal or hepatic impairment and for dosage modification due to drug interactions.

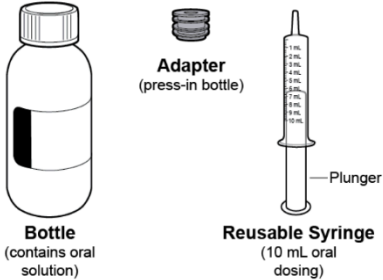
Crohn's Disease

- Adults: The recommended induction dosage of upadacitinib is 45 mg tablet once daily for 12 weeks. The recommended maintenance dosage of upadacitinib is 15 mg tablet once daily. A maintenance dosage of 30 mg once daily may be considered for patients with refractory, severe, or extensive disease. Discontinue upadacitinib if an adequate therapeutic response is not achieved with the 30 mg dosage. Use the lowest effective dosage needed to maintain response.
- See the Full Prescribing Information for the recommended dosage in patients with renal or hepatic impairment and for dosage modification due to drug interactions.

Proposed: Polyarticular Juvenile Idiopathic and Pediatric Patients with Psoriatic Arthritis

The recommended dosage is based on body weight:

Patient Weight	Upadacitinib oral solution	Upadacitinib tablet
10 kg to less than 20 kg	3 mg (3 mL oral solution) twice daily	Not recommended

	<table border="1"> <tr> <td>20 kg to less than 30 kg</td> <td>4 mg (4 mL oral solution) twice daily</td> <td>Not recommended</td> </tr> <tr> <td>30 kg and greater</td> <td>6 mg (6 mL oral solution) twice daily</td> <td>15 mg (one 15 mg tablet) once daily</td> </tr> </table>	20 kg to less than 30 kg	4 mg (4 mL oral solution) twice daily	Not recommended	30 kg and greater	6 mg (6 mL oral solution) twice daily	15 mg (one 15 mg tablet) once daily
20 kg to less than 30 kg	4 mg (4 mL oral solution) twice daily	Not recommended					
30 kg and greater	6 mg (6 mL oral solution) twice daily	15 mg (one 15 mg tablet) once daily					
How Supplied	Upadacitinib extended-release tablets are supplied as: • 15 mg: purple, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with 'a15' on one side. 30 tablets in a bottle; NDC: 0074-2306-30. • 30 mg: red, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with 'a30' on one side. 30 tablets in a bottle; NDC: 0074-2310-30. • 45 mg: yellow to mottled yellow, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with 'a45' on one side. 28 tablets in a bottle; NDC: 0074-1043-28. Proposed: upadacitinib oral solution is supplied as a 1 mg/mL oral solution in HDPE bottles. Each bottle contains a labeled volume of 180 mL of solution. The bottle is packaged in a carton with one press-in bottle adapter and one 10 mL oral dosing syringe; NDC: 0074-2320-01						
Storage	Upadacitinib extended-release tablets • Store at 2°C to 25°C (36°F to 77°F). • Store in the original bottle in order to protect from moisture. Proposed: upadacitinib oral solution • Store between 2°C to 30°C (36°F to 86°F). • Discard remaining oral solution 60 days after opening the bottle.						
Container Closure/Device Constituent	Proposed: upadacitinib oral solution  The diagram illustrates the components for the proposed upadacitinib oral solution. On the left is a bottle labeled 'Bottle (contains oral solution)'. In the center is an 'Adapter (press-in bottle)'. On the right is a 'Reusable Syringe (10 mL oral dosing)' with a 'Plunger'.						
Intended Users	Patients; caregivers; healthcare providers						
Intended Use Environment	Home; clinic						

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On February 15, 2024, we searched previous DMEPA reviews relevant to this current review using the term, "upadacitinib" AND "oral solution". Our search identified one memo. See details below.

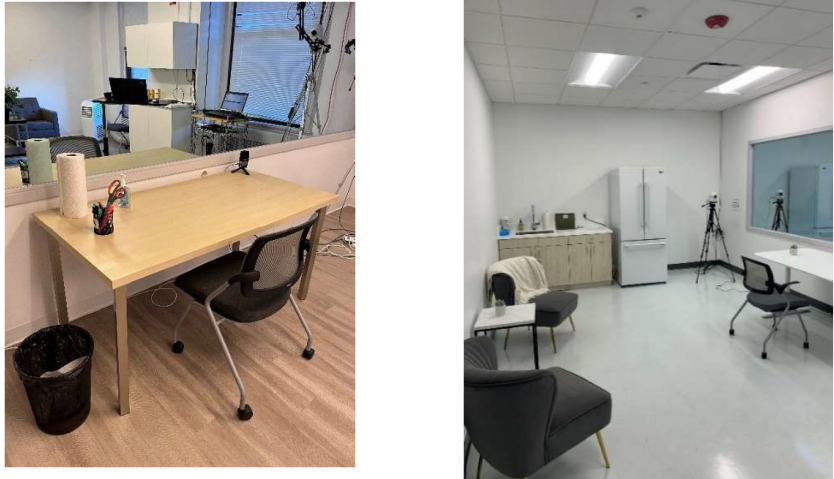
- On December 6, 2022, the Applicant submitted an HF validation study protocol for upadacitinib oral solution for Agency feedback under IND 114717. Subsequently, on July 19, 2023, we noted that the Applicant completed the HF validation study prior to completion of our protocol review, as the Applicant submitted their HF validation study results report as part of their marketing application on June 28, 2023, under NDA 218347 for upadacitinib oral solution. As such, we determined that it was not necessary to review the HF validation study protocol and that it should be withdrawn.
- The abovementioned Applicant's June 28, 2023 HF validation study results report, submitted with their new drug application under NDA 218347, is the topic of this review.

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

2.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design. See Appendix A for more details on the study design.

Table 3. Study Methodology for the Human Factors (HF) Validation Studies	
Study Design Elements	Details provided by Applicant
User Groups	• Adolescents and their lay caregivers: 15 participants of each • Lay caregivers: 16 participants • Healthcare providers: 15 participants
Training	Participants did not receive training.
Test Environment	The test environment simulated a home environment by supplying coming household items (e.g., pens, tissues, trash can) and indoor lighting levels. No specific effort was made to control distractions that might have occurred naturally during testing (e.g., ambient noise, participant's cell phone ringing). The room also contained furnishings such as a table, chairs, sink, etc.

	
Sequence of Study	1. Two simulated use scenarios: 3 mL and 12 mL simulated use scenarios. The order in which each participant performed each dose was counterbalanced. Even-numbered participants performed the high dose scenario first and low dose scenario second. Odd-numbered participants performed the low dose scenario first and the high dose scenario second. 2. Root cause analysis interview 3. Knowledge tasks assessment 4. Root cause analysis interview

2.2 DISCUSSION OF STUDY METHODOLOGY

During the course of our review of the HF validation study results, we noted that there were methodology issues. Such issues include letting caregivers participate in the study with the adolescent participants, including leading language (i.e., starting each knowledge task assessment with “*According to the materials*”) and using water instead of a placebo that represents the physiochemical properties of the drug product. However, since the user interface is one that is often used over the counter and includes tasks similar to those commonly used over the counter products, we determined that the methodology issues did not preclude our review of the HF validation study results.

3 RESULTS AND ANALYSES

In this section, we have carefully reviewed each reported issue (i.e., use errors), the Applicant’s URRAs, the participants’ subjective feedback, the Applicant’s root cause analysis and the Applicant’s comments to determine if the results indicate that the user interface has been appropriately designed to support the safe and effective use of the proposed product. In Table 4 below, we document our points of dissent with the Applicant’s findings. Additionally, Appendix D provides the observed use task and knowledge task issues where we agree with the Applicant’s conclusions and have no further recommendations or comments.

Table 4. Focused Analysis of Use Errors, Use Difficulties and DMEPA’s Recommendations

UE = use error; CC = close call; UD = use difficulty; URRRA = use-related risk analysis; RCA = root cause analysis; IFU = instructions for use; HFVS = Human Factors Validation Study
 Participants ID: AP = adult participant; ACP = adolescent-caregiver pair participants; CP = caregiver participant; HCP: healthcare provider participant

Information Supplied by Applicant	DMEPA’s Findings and Recommendations				
Knowledge task: According to the materials, can you use other syringes with this product? (Answer: No – use only the syringe provided). <table border="1" data-bbox="82 527 451 590"> <tr> <td>Errors:</td> <td>Participant Type:</td> </tr> <tr> <td>UE (n = 6)</td> <td>ACP = 2; CP = 4</td> </tr> </table> Observed error(s): participants stated they could use other syringes. Relevant RCA/Subjective Feedback/Observation: • Incorrect mental model: Participants who did not refer to the instructions assumed they could use other syringes. • Abnormal use: Participant stated although the IFU instructs to only use the syringe provided they would still use another syringe if needed. • Lack of information saliency: Participant stated that another syringe that fits the adapter could be used, since they could not see the relevant instructions in the IFU. The participant was looking for the relevant language under “Preparing Rinvoq” in the IFU. Based on the Applicant’s URRRA, performing this task incorrectly or not at all may result in spillage and leaks, exposure to degraded drug product leading to flare of disease state, and exposure to unknown substance leading to trauma.	Errors:	Participant Type:	UE (n = 6)	ACP = 2; CP = 4	
Errors:	Participant Type:				
UE (n = 6)	ACP = 2; CP = 4				
Applicant’s Comments and Proposed Post-HFSS Mitigations: None	Based on the subjective feedback (participant could not see the statement, “Only use the syringe provided”, located in the “Important Information You Need to Know Before Giving Rinvoq” section of the IFU and they expected the information to be located in the “Preparing Rinvoq” section, which only states, “Only use the syringe if it is clean and dry.”) and our overall assessment of the labeling, we find that the location and prominence of the relevant information can be improved to facilitate identification by users. We provide our recommendations in Table A to address these concerns. We have determined that this change can be implemented without submitting additional HF testing data for Agency review.				
Knowledge task: According to the materials, what colors should the drug product be? (Answer: colorless to light yellow). <table border="1" data-bbox="82 1444 451 1507"> <tr> <td>Errors:</td> <td>Participant Type:</td> </tr> <tr> <td>UE (n = 5)</td> <td>ACP = 3; CP: 2</td> </tr> </table> Observed error(s): Participants stated that the medication should be clear. Relevant RCA/Subjective Feedback/Observation: • Incorrect mental mode: Participants who did not refer to the IFU stated that the color should be clear, because that was the color of the [placebo] medication they administered. One participant assumed the color should be “white” like water. • Lack of information saliency: Participant could not locate the relevant information, since they could not see the instructions in the IFU. The participant was looking for the instruction in the “Preparing Rinvoq” section of the IFU.	Errors:	Participant Type:	UE (n = 5)	ACP = 3; CP: 2	
Errors:	Participant Type:				
UE (n = 5)	ACP = 3; CP: 2				

Based on the Applicant's URRR, performing this task incorrectly or not at all may result in exposure to/administration of unknown substances.					
Applicant's Comments and Proposed Post-HFSS Mitigations: None	Based on the subjective feedback (participant could not see the statement, (b) (4) located in the "Important Information You Need to Know Before Giving Rinvoq" section of the IFU and they expected the information to be located in the "Preparing Rinvoq section") and our overall assessment of the labeling, we find that the location of the relevant information can be improved to facilitate identification by users. We provide our recommendations in Table A to address these concerns. We have determined that this change can be implemented without submitting additional HF testing data for Agency review.				
Knowledge task: According to the materials, when giving a new dose, can the syringe be used if it is still wet from being rinsed? (Answer: No). <table border="1" data-bbox="82 688 451 751"> <tr> <td>Errors:</td> <td>Participant Type:</td> </tr> <tr> <td>UE (n = 2)</td> <td>CP: 2</td> </tr> </table>	Errors:	Participant Type:	UE (n = 2)	CP: 2	
Errors:	Participant Type:				
UE (n = 2)	CP: 2				
Observed error(s): One participant answered, "yes" and another answered that they assumed they could place the syringe in the carton back without rinsing it.					
Relevant RCA/Subjective Feedback/Observation: • Test artifact: Participant misunderstood the question and thought the word "wet" in the knowledge task assessment meant that medication was remaining in the syringe that should be given to the patient. • Lack of information saliency: Participant could not see the relevant information in the IFU and assumed it would be located in the "Important Information You Need to Know Before Giving Rinvoq" section of the IFU.					
Based on the Applicant's URRR, performing this task incorrectly or not at all may result in infection.					
Applicant's Comments and Proposed Post-HFSS Mitigations: None	Based on the subjective feedback (the participants could not see the relevant information) and our overall assessment of the labeling, we find that the prominence of the relevant information can be improved to facilitate identification by users. We provide our recommendations in Table A to address these concerns. We have determined that this change can be implemented without submitting additional HF testing data for Agency review.				
Knowledge task: According to the materials, what should be provided to the patient after the entire prescribed dose is administered? (Answer: A drink of water) <table border="1" data-bbox="82 1491 483 1554"> <tr> <td>Errors:</td> <td>Participant Type:</td> </tr> <tr> <td>UE (n = 6)</td> <td>CP = 3; ACP = 1; HCP = 2</td> </tr> </table>	Errors:	Participant Type:	UE (n = 6)	CP = 3; ACP = 1; HCP = 2	
Errors:	Participant Type:				
UE (n = 6)	CP = 3; ACP = 1; HCP = 2				
Observed error(s): participants answered that they would not give anything; discard the product; or had no response.					
Relevant RCA/Subjective Feedback/Observation: • Incorrect mental model: participants assumed nothing should be provided to the patient after administering the dose. These participants did not refer to the IFU and one stated that they typically refer to the IFU but did not during the study because they weren't actually administering the medication to their child. • Test artifact: Participants misunderstood the question and thought the question was related to disposal after dose administration.					

Lack of information saliency: participant could not see the relevant instructions in the IFU.	
Based on the Applicant's URRRA, performing this task incorrectly or not at all may result in residue on sensitive mucosa/dentin leading to trauma.	
Applicant's Comments and Proposed Post-HFSS Mitigations: None	Based on the subjective feedback (participant could not see the relevant instruction) and our overall assessment of the labeling, we find that the prominence and location of the relevant information can be improved to facilitate identification by users. We provide our recommendations in Table A to address these concerns. We have determined that this change can be implemented without submitting additional HF testing data for Agency review.

3.1 ANALYSIS OF THE REMAINING IDENTIFIED ISSUES

The HF validation study reports showed issues with the tasks evaluated by simulated use and knowledge task assessments listed in Appendix D. However, based on our review of the available assessment of these identified issues, the available participants' subjective feedback (including when participants' subjective feedback did not indicate any potential issue with the user interface), the Applicant's root cause analysis, our evaluation of the residual risks, we find the proposed user interface has been appropriately designed and we did not identify recommendations to address the identified issues with the tasks in Appendix D.

3.2 LABELS AND LABELING

Table A below includes the identified medication error issues with the submitted IFU based on the HF study results, our rationale for concern, and the proposed recommendations to minimize the risk for medication errors. Additionally, we note that the DMEPA 1 naming and labeling review team evaluated product specific label and labeling under a separate cover.²

² Vee, Sarah. Label and labeling review for upadacitinib NDA 218347. Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JAN 30. TTT ID #: 2023-5320.

Table A: Identified Issues and Recommendations for AbbVie, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU)			
1.	Step 1, "Check the prescribed dose." states, (b) (4) (b) (4) and Step 12, "Give the oral solution" states, (b) (4) (b) (4) However, according to the prescribing information, the recommended upadacitinib oral solution dose volume (i.e., 3 mL, 4 mL, and 6 mL) (b) (4) (b) (4)	This IFU language does not align with the recommended doses, which may cause confusion and result in medication errors.	Remove the statements, (b) (4) (b) (4) and (b) (4) (b) (4)

2.	The location and prominence of the instructions regarding only using the provided syringe can be improved.	Per the URRA, if the user does not use the syringe provided there is risk of spillage and leaks, exposure to degraded drug product leading to flare of disease state, and exposure to unknown substance leading to trauma. The HF validation study results identified subjective feedback that indicated a participant could not see the statement, "Only use the syringe provided" located in the "Important Information You Need to Know Before Giving Rinvoq" section of the IFU and they expected the information to be located in the "Preparing Rinvoq section, which does not contain relevant instructions.	Include instructions on only using the syringe provided in the "Preparing Rinvoq" section. For example, add the instruction "Only use the syringe provided" to the bulleted statement under "Step 1. Check the prescribed dose".
3.	The IFU does not include active instructions for the user to inspect the medication and its color. Instead, the IFU states in the "Important Information You Need to Know Before Giving Rinvoq" that the (b) (4) . Additionally, this information lacks prominence.	Per the URRA, if the user does not inspect the medication color there is risk of exposure to/administration of unknown substances. The HF validation study results identified subjective feedback that indicated a participant could not locate the relevant information, since they could not see the instructions in the IFU. The participant was looking for the instruction in the "Preparing Rinvoq" section of the IFU.	Include instructions on inspecting the medication color in the "Preparing Rinvoq" section. For example, include these instructions with Step 2, "Check expiration date."

4.	The statement, "Only use the syringe if it is clean and dry." lacks prominence.	Per the URRRA, if the user uses a wet syringe there is risk of infection. The HF validation study results identified subjective feedback that indicated a participant could not see the relevant information in the IFU.	Increase the prominence of the statement, "Only use the syringe if it is clean and dry."
5.	The Step 12 statement, "(b) (4) give the child a drink of water and (b) (4) should be removed (see recommendation #1 for more information).	Starting the statement instructing the patient to drink water after administration with an (b) (4) may cause confusion.	Revise the statement to "Give the child a drink of water." See recommendation #6 for more information.

6.	The location and prominence of the instructions regarding providing water to patients after dose administration can be approved.	Per the URRA, if the patient does not drink water there is risk of residue on sensitive mucosa/dentin. The HF validation study results identified subjective feedback that indicated a participant could not see the Step 12 statement, (b) (4) give the child a drink of water (b) (4) "	See recommendation #5 and increase the prominence of the instructions, "Give the child a drink of water." by creating a separate step. Include an image corresponding with this step.

4 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation studies demonstrated several use errors with critical tasks. Based on our review of the available participants' subjective feedback and root cause analysis, we identified additional risk mitigations to address the use errors with labels and labeling. Above, we have provided recommendations in Table A for the Applicant. We ask that the Division of Rheumatology and Transplant Medicine (DRTM) convey Table A in its entirety to the Applicant. These changes can be implemented without submitting additional HF testing data for Agency review.

4.1 RECOMMENDATIONS FOR ABBVIE, INC.

Our evaluation of your human factors (HF) validation studies for upadacitinib oral solution user interface indicates that there are additional mitigations that can be implemented to address use errors that occurred with critical tasks. We provide recommendations in Table A, and we recommend that you implement these recommendations and submit the revised labels and labeling for our review prior to the approval of this NDA. We have determined that, in this instance, you may implement these revisions without submitting additional human factors testing data for Agency review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. HUMAN FACTORS STUDY RESULTS REPORT

Human factors validation study results: [\\CDSESUB1\EVSPROD\nda218347\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ \(b\) \(4\) 5354-other-stud-rep\human-factors-report\oral-solution-hf-rpt.pdf](\\CDSESUB1\EVSPROD\nda218347\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ (b) (4) 5354-other-stud-rep\human-factors-report\oral-solution-hf-rpt.pdf)

Use-related risk analysis: [\\CDSESUB1\EVSPROD\nda218347\0011\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ \(b\) \(4\) 5354-other-stud-rep\agency-response-qa-2023-nov-30\regional-information-urrareport.pdf](\\CDSESUB1\EVSPROD\nda218347\0011\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ (b) (4) 5354-other-stud-rep\agency-response-qa-2023-nov-30\regional-information-urrareport.pdf)

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On November 30, 2023, we issued an information request (IR) asking the Applicant to:

- provide their use-related risk analysis.
- clarify why the user interface does not include the adapter inserted in the bottle.

On December 4, 2023, the Applicant provided an acceptable response that can be accessible in EDR via: [\\CDSESUB1\EVSPROD\nda218347\0011\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ \(b\) \(4\) 5354-other-stud-rep\agency-response-qa-2023-nov-30\agency-response-qa-2023-nov-30.pdf](\\CDSESUB1\EVSPROD\nda218347\0011\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ (b) (4) 5354-other-stud-rep\agency-response-qa-2023-nov-30\agency-response-qa-2023-nov-30.pdf) and [\\CDSESUB1\EVSPROD\nda218347\0011\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ \(b\) \(4\) 5354-other-stud-rep\agency-response-qa-2023-nov-30\regional-information-urrareport.pdf](\\CDSESUB1\EVSPROD\nda218347\0011\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ (b) (4) 5354-other-stud-rep\agency-response-qa-2023-nov-30\regional-information-urrareport.pdf)

On March 8, 2024, we issued an IR asking the Applicant to provide the:

- clinical impact of errors listed in the use-related risk analysis
- potential hazards/harm, severity and task categorization (critical vs non-critical) for the task, "According to the materials what colors should the drug be?"

On March 12, 2024, the Applicant provided an acceptable response that can be accessible in EDR via: [\\CDSESUB1\EVSPROD\nda218347\0026\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ \(b\) \(4\) 5354-other-stud-rep\agency-response-qa-2024-mar-08\agency-response-qa-2024-mar-08.pdf](\\CDSESUB1\EVSPROD\nda218347\0026\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ (b) (4) 5354-other-stud-rep\agency-response-qa-2024-mar-08\agency-response-qa-2024-mar-08.pdf)

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following upadacitinib oral solution labels and labeling submitted by AbbVie, Inc.

- Container labels (submitted on February 9, 2024)
- Blister labeling (submitted on February 9, 2024)
- Carton labeling (submitted on February 9, 2024)
- Prescribing information (image now shown, cross referenced from NDA 218347, January 5, 2024) is available from:
<\\CDSESUB1\evsprod\NDA218347\0016\m1\us\114-labeling\draft\labeling>
- Instructions for use (image now shown, submitted on June 28, 2023):
<\\CDSESUB1\EVSPROD\nda218347\0001\m1\us\114-labeling\draft\labeling\instructions-for-use-upadacitinib.pdf>

Container Label



³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.



APPENDIX D. DETAILED LIST OF USE ERRORS, USE DIFFICULTIES, AND CLOSE CALLS FROM SECTION 3.1

- Use scenarios:
 - Insert adapter: there were ten use errors and three use difficulties observed for this task. For the use errors, the root cause analysis (RCA) indicated incorrect mental model (eight participants thought that they did not need the adapter to withdraw medication) and negative transfer (one participants stated that their medications at home come with the adapter inserted or the syringe fits in the bottle opening), and test artifact (one participant was nervous about being recorded and did not see the adapter). For the use difficulties, the RCA indicated that participants initially had difficulty pressing down on the adapter until it was flush with the top of the bottle but were eventually able to complete the task. Based on our review of the user interface, we did not identify any additional mitigations to address these use errors and difficulties and have no recommendations at this time.
 - Expel air from the syringe: there were three use errors. The RCA indicated incorrect mental model (one participant was initially unsure of how to measure the dose and drew up air in the syringe before pushing the plunger to their dose of 3 mL and one participant filled the syringe with air because they were a step ahead and were already thinking about drawing up the medication despite not

having attached the syringe to the adapter) and test artifact (the participant filled the syringe with air up to their dose to show their granddaughter what that would look like). Based on our review of the user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.

- Insert syringe tip into adapter: see use errors with above task, "Insert adapter". There was also one use error in which the user pressed on the adapter via the inserted syringe because the adapter was not flush with the top of the bottle and the adapter fell into the bottle. The RCA indicated negative transfer in which the user was used to applying more force to insert the adapter and expected a "click" to indicate adapter insertion. Based on our review of the user interface, we did not identify any additional mitigations to address this use error and have no recommendations at this time.
- Invert bottle with syringe attached: see use errors with above task, "Insert adapter". There were also four other use errors and one close call observed with this task. For the use errors, the RCA indicated incorrect mental model in which participants assumed they could draw the medication without inverting the bottle. For the close call, the RCA indicated incorrect mental model since the participant initially thought keeping the bottle horizontal would be sufficient but realized they needed to invert the bottle with the syringe inserted and self-corrected. Based on our review of the user interface, we did not identify any additional mitigations to address these use errors and close call and have no recommendations at this time.
- Draw solution into syringe while removing large air bubbles if present: there were six use errors and four use difficulties. One use error was due to the above use errors "Insert adapter" and "Invert bottle with syringe attached" that prevented tapping the bubbles to the top of the syringe. For the other use errors, the RCA indicated incorrect mental model and incorrect technique (one participant kept pulling out the syringe from the adapter while trying to pull up the medication and then they forgot to place the initial 10 ml into the cup and instead kept pulling the syringe with air up to the 2 mL mark), test artifact (one participant did not feel they needed to read the instructions for use (IFU) "several times" as they normally would since this was a testing session, and incorrect mental model (three participants who did not read the instructions for use assumed the air bubbles were not large enough for which to account). For the use difficulties, the RCA indicated information saliency (one participant had to read the IFU several times before proceeding), test artifact (one participant missed the associated step since they were nervous due to the testing environment and their glasses were fogging up), and incorrect technique (one participant squeezed the bottle when drawing medication and one participant pulled the syringe out of the adapter). Based on our review of the user interface,

we did not identify any additional mitigations to address these use errors and difficulties and have no recommendations at this time.

- Adjust syringe plunger to desired dose (under 90% of dose or over 110% of dose): there were six use errors. The RCA indicated test artifact (one participant stated they usually need to read the instructions “seven to eight time” prior to giving medication but did not during the use scenarios since they did not feel that they had enough time during the test session) and incorrect technique and mental model (participants did not remove the large air bubble or only used one syringe to measure their 12 mL dose). Based on our review of the user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.
- Restore bottle to upright position and remove syringe from adapter
- Check amount of medication in syringe
- Administer oral dose to patient
- If dose requires more than one syringe, repeat steps for second syringe; does not administer a second syringe worth of medication is unnecessary
- Close the bottle without removing adapter
- Knowledge task assessments
 - Question: According to the materials, what should you do with the medication if it is expired? Answer: Do not use if expired.
 - Question: According to the materials, who should the product be kept away from? Answer: Children.
 - Question: According to the materials, what should you do if your child takes too much or not enough oral solution? Answer: contact your healthcare provider.
 - Question: According to the materials, what should you do if your child takes too much or not enough oral solution? Answer: Contact your healthcare provider.
 - Question: According to the materials, what should be provided to the patient after the entire prescribed dose is administered? Answer: A drink of water.
 - Question: According to the materials, how should you store the bottle between uses? Answer: Mentions all - upright; either: in carton or in a dark place; in recommended temperature range.
 - Question: According to the materials, how should the syringe be cleaned and dried between uses? Answer: Mentions all of these - remove the plunger from the syringe; rinse both parts with water; do not use soap; do not put the syringe in the dishwasher; air dry.
 - Question: according to the materials, how should the syringe be stored between uses? Answer: Mentions both - clean place/surface and dry place/surface.
 - Question: According to the materials, when giving a new dose, can the syringe be used if it is still wet from being rinsed? Answer: No.

- Question: According to the materials, what should you do with the syringe after you have finished the bottle? Answer: Dispose of the syringe (including place in trash).

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: March 19, 2024

To: Suprat Saely
Regulatory Project Manager
**Division of Rheumatology and Transplant Medicine
(DRTM)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nyedra W. Booker, PharmD, MPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kyle Snyder, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name), Dosage Form and Route, Application Type/Number and Supplement Number: RINVOQ (upadacitinib) extended-release tablets, for oral use, NDA 211675/S-021 and S-022

RINVOQ (b) (4) (upadacitinib) oral solution, NDA 218347

Applicant: AbbVie Inc.

1 INTRODUCTION

On June 28, 2023, AbbVie Inc. submitted for the Agency's review an Efficacy Supplement to the New Drug Application (NDA 211675) for RINVOQ (upadacitinib) extended-release tablets, for oral use. As stated by the Applicant:

The purpose of this submission is to submit an efficacy supplement to New Drug Application (sNDA) 211675 for RINVOQ (upadacitinib) for the treatment of patients with polyarticular (b) (4) juvenile idiopathic arthritis (b) (4), request for priority review designation and request for postmarketing requirement (PMR) 3680-2 release.

On June 28, 2023, the Applicant also submitted for the Agency's review a Type 3 New Drug Application (NDA 218347) for RINVOQ (b) (4) (upadacitinib) oral solution for a new 1 mg/mL oral solution formulation of upadacitinib in support of the polyarticular (b) (4) juvenile idiopathic arthritis (b) (4) and juvenile psoriatic arthritis (JPsA) indications.

RINVOQ (upadacitinib) extended-release tablets, for oral use was approved on August 16, 2019, and is a Janus kinase (JAK) inhibitor indicated for the treatment of:

- adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers.
- adults with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers.
- adults and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable.
- adults with active ulcerative colitis who have had an inadequate response or intolerance to one or more TNF blockers.
- adults with active Crohn's disease who have had an inadequate response or intolerance to one or more TNF blockers.
- adults with ankylosing spondylitis who have had an inadequate response or intolerance to one or more TNF blockers.
- adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation who have had an inadequate response or intolerance to one or more TNF blockers.

This review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Rheumatology and Transplant Medicine (DRTM) on July 11, 2023, for DMPP and OPDP to review the Applicant's proposed MG and IFU for RINVOQ (upadacitinib) extended-release tablets, for oral use and RINVOQ (b) (4) (upadacitinib) oral solution.

2 MATERIAL REVIEWED

- Draft RINVOQ (upadacitinib) extended-release tablets, for oral use and RINVOQ (b) (4) (upadacitinib) oral solution MG and IFU received on June 28, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 8, 2024.
- Draft RINVOQ (upadacitinib) extended-release tablets, for oral use and RINVOQ (b) (4) (upadacitinib) oral solution PI received on June 28, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 8, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss.

In our review of the MG and IFU, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

- Our review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: March 12, 2024
Requesting Office or Division: Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number: NDA 218347
Product Name, Dosage Form, and Strength: upadacitinib oral solution, 1 mg/mL
Applicant/Sponsor Name: Abbvie
TTT ID #: 2023-5320-1
DMEPA 1 Safety Evaluator: Sarah K. Vee, PharmD
DMEPA 1 Team Leader (Acting): Damon Birkemeier, PharmD, FISMP, NREMT

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on February 9, 2024 for upadacitinib. The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container label and carton labeling for upadacitinib (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

In response to our recommendations, Abbvie stated that, "... *Abbvie notes a concern related to the potential for ink solvents common in many permanent markers leaching through the* (b) (4) *primary container,....*" We requested OPQ to opine on the validity of the Abbvie's concern and OPQ stated that it could potentially be an issue. We continue to recommend that Abbvie provide a space to record the open date on the container label since the carton may be discarded and Abbvie did not provide concrete data supporting potential for markers leaching into the container.

^a Vee, S. Label and Labeling Review for upadacitinib (NDA 218347). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JAN 30. TTT ID No.: 2023-5320.

2 CONCLUSION

The container label and carton labeling are unacceptable from a medication error perspective. The prescribing information indicates that Rinvoq (b) (4) and Rinvoq are not substitutable; however, the principal display panel of the container labels and carton labeling does not convey this information. Absence of this information may lead to wrong drug/dose medication errors and is inconsistent with the prescribing information. We recommend including a warning on the container labels and carton labeling- "Rinvoq (b) (4) and Rinvoq are not substitutable."

3 RECOMMENDATIONS FOR ABBVIE

A. Container Label

1. We recommend relocating the warning on the container labels: "Rinvoq (b) (4) and Rinvoq are NOT substitutable." directly beneath the strength statement. Additionally, we recommend adding a similar statement to the Rinvoq extended-release tablets container label (e.g., "Rinvoq and Rinvoq (b) (4) are NOT substitutable").
2. We acknowledge your concern "*related to the potential for ink solvents common in many permanent markers leaching through the (b) (4)* primary container". We discussed your concern with our OPQ colleagues, and we are not aware of any data supporting your concern with high-density polyethylene (HDPE) bottles. Additionally, we acknowledge that the "Date Opened" statement has been added to the carton labeling, however, we are making this recommendation for the container label in the instances the carton labeling is discarded. From a medication error perspective, we continue to recommend providing space for the "Date Opened" to be recorded on the container label, but we defer this decision to you. If you decide not to include this statement on the container label, we recommend you consider alternate ways to make this statement more prominent on the carton labeling to help ensure the information is acknowledged and filled out and the carton labeling is not discarded (e.g., consider boxing the information and/or relocating the information to a more prominent location on the side panel).

B. Carton Labeling

1. As currently presented, the carton labeling does not indicate that the proposed product is not substitutable with Rinvoq extended-release tablets for oral use. Inadvertent substitution can lead to medication errors such as, but not limited to, wrong drug errors leading to no treatment effect, overdose or underdose leading to adverse events or lack of efficacy. We recommend including a warning - "Rinvoq (b) (4) and Rinvoq are NOT substitutable." directly beneath the strength statement on the carton labeling.

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

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

Memorandum

Date: March 12, 2024

To: Suprat Saely, Regulatory Project Manager
Division of Rheumatology and Transplant Medicine (DRTM)

Jane Filie, Associate Director for Labeling, DRTM

From: Kyle Snyder, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for RINVOQ® (upadacitinib) extended-release tablets, for oral use (Rinvoq); and RINVOQ® (b) (4) (upadacitinib) oral solution (Rinvoq)

NDA: 211675/S-021 and S-022; and 218347

Background:

In response to DRTM's consult requests dated July 11, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for supplemental NDA 211675/S-021 for Rinvoq which proposes addition of an indication for polyarticular (b) (4) juvenile idiopathic arthritis; supplemental NDA 211675/S-022 which proposes updates based on required pediatric assessments; and NDA 218347 which proposes a new dosage form. OPDP has also reviewed Instructions for Use (IFU) and carton and container labels that were submitted under NDA 218347.

PI/Medication Guide/IFU:

OPDP's review of the proposed PI and Medication Guide is based on the draft labeling emailed to OPDP on March 8, 2024, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide and IFU, and comments will be sent under separate cover.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on February 9, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at 240-402-8792 or kyle.snyder@fda.hhs.gov.

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	January 30, 2024
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	NDA 218347
Product Name, Dosage Form, and Strength:	upadacitinib oral solution, 1 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Abbvie, Inc
FDA Received Date:	June 28, 2023, July 14, 2023, November 22, 2023, January 5, 2024
TTT ID #:	2023-5320
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader (Acting):	Damon Birkemeier, PharmD, FISMP, NREMT

1 REASON FOR REVIEW

As part of the approval process for upadacitinib oral solution, the Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the proposed upadacitinib prescribing information, medication guide, instructions for use, container label, and carton labeling for areas of vulnerability that may lead to medication errors.

In addition, on June 28, 2023, and June 30, 2023, Abbvie, Inc submitted Efficacy Supplements (NDA 211675/S-021 & NDA 211675/S-022) for Rinvoq (upadacitinib) extended-release tablets to add indications of polyarticular (b) (4) juvenile idiopathic arthritis (b) (4) and juvenile psoriatic arthritis (JPsA), which are being reviewed under separate cover.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION & RECOMMENDATIONS

Abbvie submitted NDA 218347 for upadacitinib oral solution (1 mg/mL), which was developed for polyarticular (b) (4) juvenile idiopathic arthritis (b) (4) and juvenile psoriatic arthritis (JPsA) indications, and for patients who are not able to swallow tablets. We note that upadacitinib was approved in extended-release tablet dosage form on August 16, 2019, for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), atopic dermatitis (AD), ankylosing spondyloarthritis (AS), non-radiographic axial spondyloarthritis (nraxSpA), ulcerative colitis (UC), and Crohn's disease (CD) under NDA 21675.

We reviewed the proposed labels and labeling for upadacitinib oral solution to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. Our evaluation of the proposed upadacitinib medication guide and instructions for use did not identify areas on vulnerability that may lead to medication errors. However, the proposed PI, container labels, and carton labeling may be improved to promote the safe use of the product from a medication error perspective.

Note that DMEPA 1 is evaluating the HF validation study results under separate cover and, based on the outcome of that review, additional label and labeling comments may be forthcoming.

4 RECOMMENDATIONS FOR DIVISION OF RHEUMATOLOGY AND TRANSPLANT MEDICINE (DRTM)

A. Prescribing Information

1. Section 2.2 and the Highlights of Prescribing Information currently state

[REDACTED] (b) (4)

We recommend revising this information to focus on RINVOO (b) (4) and to clarify that RINVOO tablets are extended-release tablets.

For example, revise to:

[REDACTED] (b) (4)

2. As currently presented, Section 2.3 and Table 1 contains the symbols, “≥” and “<”. We recommend replacing the symbols, “≥” and “<” with the intended meanings to avoid confusion.

5 RECOMMENDATIONS FOR ABBVIE, INC

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. Note that DMEPA 1 is evaluating the HF validation study results under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming.
2. As currently presented, there is no space for end-users to write the beyond-use date which is the date the opened product must be discarded. Since the product has a different expiration date after opening, the container label and the carton labeling should have a designated space and format for end-users to write the beyond-use date to minimize the risk of deteriorated drug medication errors. We recommend adding a space for the end- user to document the date that each bottle is opened: “Discard unused portion of the bottle 60 days after first opening. Date of first Use: __/__/__.
3. Revise the statement, [REDACTED] (b) (4) to “Recommended dosage: see prescribing information”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for upadacitinib received on January 5, 2024 from Abbvie, Inc.

Table 2. Relevant Product Information for upadacitinib		
Initial Approval Date	N/A	
Active Ingredient	upadacitinib	
Indication	• Patients 2 years of age and older with active juvenile psoriatic arthritis. <u>Limitations of Use</u> RINVOO (b) (4) is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine. • Patients 2 years of age and older with active polyarticular (b) (4) juvenile idiopathic arthritis who have had an inadequate response or intolerance to one or more TNF blockers. <u>Limitations of Use</u> RINVOO (b) (4) is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine.	
Route of Administration	oral	
Dosage Form	oral solution	
Strength	1 mg/mL	
Dose and Frequency	<u>Juvenile Psoriatic Arthritis and Polyarticular (b) (4) Juvenile Idiopathic Arthritis</u>	
	Patient Weight	Dosing Regimen
	10 to < 20 kg	3 mg (3 mL oral solution) twice daily
	20 to < 30 kg	4 mg (4 mL oral solution) twice daily
	≥ 30 kg	6 mg (6 mL oral solution) twice daily
	(b) (4)	

Table 2. Relevant Product Information for upadacitinib	
How Supplied	1 mg/mL oral solution in HDPE bottle of 180 mL packaged in a carton with one press-in bottle adapter and one 10 mL oral dosing syringe.
Storage	• Store between 2°C to 30°C (36°F to 86°F). • Discard remaining oral solution after 60 days of opening the bottle.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following upadacitinib labels and labeling submitted by Abbvie, Inc.

- Container label received on June 28, 2023
- Carton labeling received on June 28, 2023
- Instructions for Use received on June 28, 2023, available from <\\CDSESUB1\evsprod\NDA218347\0001\m1\us\114-labeling\draft\labeling>
- Prescribing Information and Medication Guide received on January 5, 2024, available from <\\CDSESUB1\evsprod\NDA218347\0016\m1\us\114-labeling\draft\labeling>

F.2 Label and Labeling Images

Container label

^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Division of Rheumatology and Transplant Medicine

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 218347, new type 3 efficacy supplement
NDA 211675/S-21, Prior Approval supplement (PAS) (efficacy)
NDA 211675/S-22, Prior Approval supplement (PAS) (efficacy)

Name of Drug: NDA 218347, Rinvoq (upadacitinib) oral solution, 1 mg/mL
NDA 211675/S-21 & S-22, Rinvoq (upadacitinib) extended-release tablets,
15mg, 30mg, and 45 mg

Applicant: AbbVie Inc.

Submission Date: June 28, 2023 (NDA 218347; NDA 211675/S-21);
June 30, 2023 (NDA 211675/S-22)

Receipt Date: June 28, 2023 (NDA 218347; NDA 211675/-21);
June 30, 2023 (NDA 211675/S-22)

Reviewer: Suprat Saely, PharmD, BCPS, FCCM, RPM

Concurrence: Margaret Kober, RPh, MPA, CPMS

Background and Summary Description:

On June 28, 2023, AbbVie submitted a new type 3 NDA 218347, proposing a new formulation of upadacitinib (1 mg/mL oral solution) for patients with polyarticular (b) (4) juvenile idiopathic arthritis (b) (4) and juvenile psoriatic arthritis (JPsA) indications who are unable to swallow the approved extended-release tablets. Concurrently on June 28, 2023, AbbVie submitted an efficacy supplement under NDA 211675/S-21 (extended-release tablets), proposing the treatment of (b) (4) in patients 2 years and older; and on June 30, 2023, AbbVie submitted an efficacy supplement under NDA 211675/S-22, proposing the treatment of JPsA in patients 2 years and older. AbbVie proposes to have both extended-release tablets and oral solution formations share the same US Prescribing Information (USPI) and Medication Guide. AbbVie submitted the proposed USPI under NDA 211675/S-21; NDA 211675/S-22 and NDA 218347 references USPI from NDA 211675/S-21. The last approved NDA 211675 labeling, updated on June 22, 2023, was a labeling supplement (S-17) to include information on improvement in fatigue scores in adult patients with ulcerative colitis treated with Rinvoq.

Review:

I compared the labeling submitted July 5, 2023, under NDA 211675, to the last approved with S-17 on June 22, 2023. Minor editorial and formatting revisions have been made throughout the document, which are acceptable. There were no changes other than those proposed with NDA 211675/S-21, NDA 211675/S-22, and NDA 218347.

Labeling discussion and reviews by the review team are currently pending.

Recommendation:

Pending approval recommendations from the review disciplines, Patient Labeling Team (PLT) and the Office of Prescription Drug Promotion (OPDP) reviews (as applicable), and labeling agreement, NDA 211675/S-21, NDA 211675/S-22, and NDA 218347 should be approved.

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