# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 213082Orig1s000

# PRODUCT QUALITY REVIEW(S)

# Office of Pharmaceutical Quality

New Drug Application (NDA) 213082
Integrated Quality Assessment

# Table of Contents

# RECOMMENDATION

| |
|---|
| ☒ Approval |
| ☐ Approval with Post-Marketing Commitment |
| ☐ Complete Response |

# NDA 213082
# Assessment #1

| | |
|---|---|
| **Drug Product Name** | Tofacitinib Oral Solution |
| **Dosage Form** | Oral solution |
| **Strength** | 1 mg/mL (as free base) |
| **Route of Administration** | oral |
| **Rx/OTC Dispensed** | Rx |
| **Applicant** | Pfizer Inc. |
| **US agent, if applicable** | N/A |

| Submission(s) Assessed | Document Date | Discipline(s) Affected |
|---|---|---|
| Original | 26-MAR-2020 | All |
| Amendment | 03-JUN-2020 | Microbiology |
| Amendment | 19-JUN-2020 | Manufacturing/Microbiology |
| Amendment | 29-JUN-2020 | Drug Product |
| | | |

**QUALITY ASSESSMENT TEAM**

| Discipline | Primary Assessment | Secondary Assessment |
|---|---|---|
| **Drug Substance** | Fred Burnett | Donna Christner |
| **Drug Product** | Zhengfang Ge | Wendy Wilson-Lee |
| **Manufacturing** | Khalid Khan | Frank Wackes |
| **Microbiology** | Dionne Coker-Robinson | Yuansha Chen |
| **Biopharmaceutics** | N/A | |
| **Regulatory Business Process Manager** | Florence Aisida | |
| **Application Technical Lead** | Craig Bertha | |
| **Laboratory (OTR)** | N/A | |
| **Environmental** | N/A | |

# EXECUTIVE SUMMARY

## I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The application is recommended for **approval**. However, there are minor labeling deficiencies that will need to be addressed.

## II. SUMMARY OF QUALITY ASSESSMENTS

### A. Product Overview

*This NDA was submitted simultaneously with an efficacy supplement for the tofacitinib tablet NDA 203214 to add an indication for Polyarticular Course Juvenile Idiopathic Arthritis (pJIA). Thus the oral solution dosage is to be an age appropriate dosage form for this patient population.*

| | |
|---|---|
| **Proposed Indication(s) including Intended Patient Population** | Polyarticular Course Juvenile Idiopathic Arthritis: XELJANZ/XELJANZ Oral Solution is indicated for the treatment of active polyarticular course juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older. |
| **Duration of Treatment** | Chronic |
| **Maximum Daily Dose** | 10 mg daily |
| **Alternative Methods of Administration** | N/A |

### B. Quality Assessment Overview

**Drug Substance:** Adequate

The synthetic scheme, control of materials, control of critical steps and intermediates, process validation studies, manufacturing process and development, characterization, impurities/degradant characterization, specifications, the analytical procedures, reference standards, container closure system, and stability data have all been cross-referenced to approved NDA 203214 and all have been determined to be adequate. For further details, see NDA 203214.

**Drug Product:** Adequate

Tofacitinib oral solution is for oral administration and is indicated for the treatment of polyarticular course juvenile idiopathic arthritis. Tofacitinib is already approved in immediate release 5 mg tablet and 11 mg extended release tablet dosage forms for treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. The current oral dosage form is formulated as an aqueous solution including the same API tofacitinib citrate, and

sweeteners (Xylitol, Sucralose), grape flavor, lactic acid (b) (4), (b) (4), and sodium benzoate (b) (4). The drug product is packaged in an HDPE bottle with a (b) (4) closure. A (b) (4) press-in bottle adapter (PIBA) and an oral syringe are included in the package.

The drug product specification includes common tests for the oral solution and is
supported by the batch data. Two identified degradation products (b) (4) (b) (4) with acceptable criteria at NMT (b) (4)% are qualified. Stability results support a 24-month expiration dating period for the drug product packaged in the original bottle and carton to protect from light and stored at controlled room temperature condition.

**Labeling:** Inadequate

The labeling is deemed not ADEQUATE as proposed until it is revised satisfactorily to meet the regulatory requirements; the deficiencies are listed below.

**Manufacturing:** Adequate

(b) (4)

(b) (4)

The manufacturing process as presented has been found adequate.

The manufacturing facilities are adequate for this application.

**Biopharmaceutics:** Choose an item.

N/A

**Microbiology (if applicable):** Adequate

The submission is **recommended** for approval on the basis of sterility assurance.

## C. Risk Assessment

| DP attribute/ CQA | Factors that may impact the CQA | O[1] | S[1, 2] | D[1] | Initial RA FMECA RPN # | Comment & considerations for risk assessment | Final RA | Comments/Lifecycle considerations |
|---|---|---|---|---|---|---|---|---|
| Appearance | • (b) (4) | 1 | 3 | 2 | 6 | (b) (4)<br>• Initial stability data do not show apparent trends for any tested parameters with the exception of (b) (4) (b) (4) | | |
| Identification | • incorrect drug formulated<br>• no API formulated | 2 | 3 | 4 | 24 | • Probability of occurrence should be low and detectability high if applicant adheres to GMPs: specification for drug substance includes specific identification testing (b) (4)<br>• (b) (4)<br>• Final drug product specification only includes *one* non-specific test for ID (not consistent with Q6A recommendation) | | |
| Assay | • incorrect amount of API formulated<br>• high impurity level of input API<br>• API degradation | 1 | 3 | 2 | 6 | • GMP adherence should prevent incorrect API amounts formulated<br>(b) (4)<br>• Applicant has not performed photostability testing as per ICH Q1B<br>• Initial stability data do not show trends for any tested parameters with the exception of (b) (4) (b) (4) | | |
| Degradation Products | • API degradation | 2 | 3 | 2 | 12 | (b) (4)<br>• Applicant has not performed photostability testing as per ICH Q1B<br>• Initial stability data do not show trends for any tested parameters with the exception of (b) (4) (b) (4)<br>• Total impurities remain below the QL for (b) months at (b) (4) | | |
| pH | • incorrect amounts of components formulated | 2 | 3 | 3 | 18 | • GMP adherence should prevent incorrect component amounts formulated (b) (4) | | |

[1] O = Probability of Occurrence; S = Severity of Effect; D = Detectability
[2] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs (thus a median value of "3" will be used throughout)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (b) (4)<br>• pH changes due to leachables (organic or elemental) or formulation component (API or excipient) degradation | | | | | (b) (4)<br>• Applicant will place a minimum of one batch of drug product up on stability per year, post approval<br>• Leachables studies did not find any elemental impurities above (b) % of the limits in ICH Q3D for parenteral formulations<br>(b) (4)<br>• The HDPE used to manufacture the CCS bottle has been approved for use for CCSs for SODFs and complies with food contact regulation of 21 CFR 177.1520, but it is unclear that it has been used for packaging aqueous-based oral solution drug products and it is not known what specific usages are allowed by the compliance with that regulation, which depends on the density and maximum extractable fraction and maximum soluble fraction test results<br>• pH does not trend on stability under long term or accelerated conditions | | |
| Density | • incorrect amounts of components formulated | 1 | 3 | 1 | 3 | • GMP adherence should prevent incorrect component amounts formulated<br>• Formulation density does not trend on stability, as expected<br>• Density of the formulation is tested at drug product release and for routine post-approval stability of annual drug product batches | | |
| Deliverable volume | • incorrect fill of bottles during manufacture<br>• leakage of filled containers prior to patient use | 2 | 3 | 2 | 12 | • Applicant applies USP <698> at release<br>• Low risk of filling issues with solution formulation on typical automated fill lines<br>• Fill weight is monitored during manufacture (see packaging batch record)<br>• Induction seal integrity is monitored during manufacturing | | |
| Microbial limits | • lower than target amount (b) (4) formulated | 2 | 3 | 2 | 12 | • GMP adherence should prevent incorrect preservative amount formulated<br>(b) (4)<br>• Annual stability batches tested annually for microbial limits<br>(b) (4) | | |
| Antimicro-bial preservative content | • lower than target amount (b) (4) formulated<br>• degradation (b) (4) (b) (4)<br>• volatile loss (b) (4) (b) (4) | 1 | 3 | 2 | 6 | • GMP adherence should prevent incorrect amount (b) (4) (b) (4)<br>• A batch of drug product with a (b) (4) concentration of only (b) (4) % of the target (i.e., at (b) (4) ) was produced; antimicrobial effectiveness testing was conducted and was said to support this low preservative level (see Ferndale product development report)<br>(b) (4) | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | [redacted] (b) (4)<br>• Induction seal integrity is monitored during manufacturing [redacted] (b) (4) | | |
| Leachables | • compounds leached from inner surface of induction seal and bottle | 2 | 3 | 5 | 30 | • Leachables studies did not find any elemental impurities above [redacted] (b) (4)% of the limits in ICH Q3D for parenteral formulations<br>• There is no testing of incoming CCS components for extractables<br>• There is no routine testing proposed for leachables on stability<br>• Bottle HDPE [redacted] (b) (4) meets some of the extractables requirements of 21 CFR 177.1520, but which parts are unclear [redacted] (b) (4) compliance with food contact regulations may suffice for safety for many liquid oral drug products (see CCS guidance)<br>• Aqueous formulations, in general, are not particularly strong extraction media [redacted] (b) (4) | 1 x 3 x 5 = 15 | Since the tofacitinib oral solution is an aqueous based product, leachables are not expected to be generated from the container closure system at levels that would affect the quality and efficacy of the drug product based on the extractable study results. Also [redacted] (b) (4) for the drug product packaged in this HDPE bottle, a semi-permeable container, is negligible based on the stability results as reviewed in section P.8. |
| Elemental impurities | • elemental impurities leached from inner surface of induction seal and bottle | 1 | 3 | 5 | 15 | • No Q3D elemental impurities were found above the reporting limits ([redacted] (b) (4)% of the limits for parenteral drug products) [redacted] (b) (4)<br>• There is no testing of incoming CCS components for elemental impurities in extractions<br>• There is no routine testing proposed for elemental impurities in formulation on stability | | |
| [redacted] (b) (4) | | 1 | 3 | 5 | 15 | [redacted] (b) (4) | | |

## D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

| |
|---|
| N/A |

2. Drug Substance Deficiencies

| |
|---|
| N/A |

3. Drug Product Deficiencies

| |
|---|
| N/A |

4. Labeling Deficiencies

| |
|---|
| Include an equivalence statement that Each mL of oral solution contains 1 mg of tofacitinib (equivalent to 1.62 mg tofacitinib citrate) |

5. Manufacturing Deficiencies

| |
|---|
| N/A |

6. Biopharmaceutics Deficiencies

| |
|---|
| N/A |

7. Microbiology Deficiencies

| |
|---|
| N/A |

8. Other Deficiencies (Specify discipline, such as Environmental)

| |
|---|
| N/A |

*Application Technical Lead Name and Date: Craig M. Bertha, CMC Lead for DPACC/DRTM 12-AUG-2020*

U.S. FOOD & DRUG ADMINISTRATION

# QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

## 1. RELATED/SUPPORTING DOCUMENTS

### A. DMFs:

| DMF # | Type | Holder | Item Referenced | Status | Date Assessment Completed | Comments |
|---|---|---|---|---|---|---|
| (b) (4) | IV | | (b) (4) | Not reviewed | | Sufficient information provided in NDA |
| | III | | | Not reviewed | | Sufficient information provided in NDA |
| | III | | | Not reviewed | | Sufficient information provided in NDA |
| | III | | | Not reviewed | | Sufficient information provided in NDA |
| | III | | | Not reviewed | | Sufficient information provided in NDA |
| | III | | | Not reviewed | | Sufficient information provided in NDA |
| | III | | | Not reviewed | | Sufficient information provided in NDA |
| | III | | | Not reviewed | | Sufficient information provided in NDA |
| | III | | | Not reviewed | | Sufficient information provided in NDA |

### B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

| Document | Application Number | Description |
|---|---|---|
| | | (b) (4) |
| IND | 70903 | Tofacitinib tablet for treatment of rheumatoid arthritis |
| | | (b) (4) |
| IND | 111294 | Tofacitinib tablet for treatment of ulcerative colitis |
| IND | 117400 | Tofacitinib oral solution for treatment of Juvenile Idiopathic Arthritis |
| IND | 203214 | Tofacitinib tablet for multiple indications |
| NDA | 208246 | Tofacitinib extended release tablet for multiple indications |

## 2. CONSULTS

| Discipline | Status | Recommendation | Date | Assessor |
|---|---|---|---|---|
| Biostatistics | N/A | | | |
| Pharmacology/Toxicology | N/A | | | |
| CDRH-ODE | N/A | | | |
| CDRH-OC | N/A | | | |
| Clinical | N/A | | | |
| Other | N/A | | | |

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# CHAPTER VII: MICROBIOLOGY

IQA ANDA Assessment Guide Reference

| | |
|---|---|
| **Product Information** | |
| **NDA Number** | 213082 |
| **Assessment Cycle Number** | 1 |
| **Drug Product Name / Strength** | Xeljanz (Tofacitinib Oral Solution 1mg/mL, 240mL presentation) |
| **Route of Administration** | Oral Solution |
| **Applicant Name** | Pfizer Inc.<br>445 Eastern Point Road,<br>Groton, Connecticut, 06340, USA |
| **Manufacturing Site** | (b) (4) |
| **Method of Sterilization** | Non-sterile Solution |

***Assessment Recommendation:*** **Adequate**

***Theme:***

| | |
|---|---|
| ☒ N/A | ☐ Depyrogenation Validation Data |
| ☐ Product Sterility Assurance | ☐ Product Release and/or Stability Specifications |
| ☐ Media Fill Data | ☐ Validation for Product Release and/or Stability Test Method |
| ☐ Validation of Product Test | ☐ Other (Requires Division Director Approval) |
| ☐ Due to Consult | |

***Justification:*** *view justification statements found at:* **Justification Statements**

| |
|---|
| N/A |
| Other (Requires Division Director Approval) – *Assessor writes-in justification here if "other" selected as theme.* |

***Assessment Summary:*** The submission is **recommended** for approval on the basis of sterility assurance.

**List Submissions Being Assessed (table):**

| Date Submitted to FDA | Date Received by FDA | Date Assigned to Reviewer |
|---|---|---|
| 03/26/2020 | 03/26/2020 | 04/03/2020 |
| 06/03/2020 | 06/03/2020 | N/A |
| 06/19/2020 | 06/19/2020 | N/A |

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

**Remarks:** The submission is in e-CTD format

**Concise Description of Outstanding Issues (List bullet points with key information and update as needed):** N/A

**Supporting Documents:** N/A

**Select Number of Approved Comparability Protocols: 0**

## S DRUG SUBSTANCE

## S.2. MANUFACTURE

## S.2.1 MANUFACTURERS

**Assessment:**

**As the drug product is non-sterile, the drug substance will not be reviewed by microbiology.**

**Adequate**

## P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –**
  Sterile, clear, colorless solution filled as a 240mL into a 250mL HDPE bottle and closed with a child resistant closure. The drug product is co-packaged with a 5mL oral dosing syringe (Manufacturer: (b) (4)) and a press-in bottle adaptor (Manufacturer: (b) (4)). Tofacitinib Oral Solution 1mg/mL is indicated for treatment of juvenile idiopathic arthritis; single-dose vials

**Drug product composition**

| Ingredient | Function | Quantity/mL |
|---|---|---|
| Tofacitinib Citrate (b) (4) | API | 1.62 mg/mL |
| Lactic Acid (b) (4) USP | (b) (4) | |
| Sodium Benzoate, NF | | |
| Xylitol, USP | | |
| Sucralose, NF | | |
| Grape Flavor, Natural (b) (4) | | |
| Hydrochloric Acid, NF | | |
| Purified Water, USP | | |

Exhibit Batch: Batch No. K061918, (b) (4)

Proposed Commercial Batch: The commercial batch size is the same as the exhibit batch size

- **Description of container closure system – Drug Product**

| Component | Description | Manufacturer |
|---|---|---|
| Bottle | 250mL HDPE Bottle | (b) (4) |
| Closure | 13mm Rubber Stopper (b) (4) | |

**Assessment:**

**Adequate**

## P.2 PHARMACEUTICAL DEVELOPMENT

## P.2.5 MICROBIOLOGICAL ATTRIBUTES

### Container/Closure and Package Integrity

**Assessment: Not applicable for non-sterile drug products.**

**Adequate**

### Antimicrobial Effectiveness Testing

Antimicrobial effectiveness testing was performed using the compendial microorganisms and in accordance with USP <51>.

(b) (4)



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(b) (4)

**Assessment:**

**Adequate**

## P.3 MANUFACTURE

### P.3.1 MANUFACTURERS

(b) (4)

Responsibilities of this facility include manufacturing and packaging of the exhibit and commercial batches and conducting stability and release testing of the finished drug product.

(b) (4)

Responsibilities of this facility include manufacturing of the oral syringe that

**Assessment:**

**Adequate**

## P.3.3 DESCRIPTION OF THE MANUFACTURING PROCESS AND PROCESS CONTROLS

### Overall Manufacturing Operation

(b) (4)

Note to Reviewer: As (b) (4) microbial limits testing is performed at release, (b) (4) hold study information will not be requested.

**Assessment:**

**Adequate**

## P.5 CONTROL OF DRUG PRODUCT

### P.5.1 SPECIFICATION

- TAMC: NMT 200 CFU/mL (as per USP <1111>)
- TYMC: NMT 20 CFU/mL (as per USP <1111>)
- *E. coli*: "Absent in 1mL" (as per USP <1111>)
- BCC: "Absent in 1mL"

**Assessment:**

**Adequate**

### P.5.2 ANALYTICAL PROCEDURES

- TAMC: USP <61>
- TYMC: USP <61>
- *E. coli*: USP <62>
- BCC: USP <60>
-

**Assessment:**

**Adequate**

**P.5.3 VALIDATION OF ANALYTICAL PROCEDURES** (Sequence No. 0005 (5) 06/03/2020 3.2.P.2 Microbiological Attributes.pdf)

**The following Information request was sent to the applicant, dated 05/28/2020:**

*Information validating the microbial testing for release and stability are not provided. Validation reports, including methods and results, should be provided for the Microbial Limits Testing (USP <61> and <62>) and for testing for B. cepacia (USP <60>).*

**Applicant response to IR, dated 06/03/2020:**

Microbial limits testing method suitability testing was performed in accordance with USP<61> and <62>. Method suitability testing for TAMC, TYMC, *E.coli*, and *BCC* testing was performed with drug product diluted in 1:10 in TSB+P/L (Tryptic Soy Broth + Polysorbate/Lecithin). After introduction of challenge organism, TAMC organisms were incubated on TSA plates at 30-35°C for NMT 3 days (for bacterial challenge organisms). TYMC organisms were incubated on SDA plates at 20-25°C for NMT 5 days (for yeast/mold challenge organisms). For TAMC/TYMC, testing organisms include: *S. aureus*, ATCC 6538, *P. aeruginosa*, ATCC 9027; *B. subtilis* ATCC 6633; *C. albicans* ATCC 10231; and *A. brasiliensis* ATCC 16404. Information on positive and negative controls was not provided; however, the acceptance criterion for is as follows: Organism recovery within 2-fold of the control (b) (4). The results are provided in Table 3.2.P.2.5-2 in Sequence No. 0005 (5) 06/03/2020 3.2.P.2 Microbiological Attributes.pdf p.2/4 and the acceptance criterion was met.

The *E. coli* (ATCC 8739) challenge was incubated on enrichment and selective media as per USP <62>. The applicant states that the acceptance criterion, “Organism Detected”, was met.

The *BCC* (ATCC 25608 and ATCC 25416) challenge was incubated on MacConkey Agar, followed by subculturing on Triple Sugar Iron Agar. The applicant states that method suitability test has been performed as per USP <60> and the acceptance criterion, “Organism Detected”, was met.

**Assessment:**

**Adequate**

## P.7 CONTAINER CLOSURE

Summary Table of the Container Closure System Proposed

**Assessment: Please see section P.1**

## P.8 STABILITY

### P.8.1 STABILITY SUMMARY AND CONCLUSION

The applicant proposes an expiry period of 24 months.

**Assessment:**

**Adequate**

### P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

Stability testing of Xeljanz (Tofacitinib Oral Solution 1mg/mL, 240mL presentation) is conducted with vials in inverted and upright orientation stored in the long-term (30°C/40% RH), accelerated (40°C/20% RH), and intermediate (35°C/35% RH) condition. For the long-term storage and intermediate storage conditions, microbiological testing is performed at release and then at 12, 24, and 36 months and AET is performed at 24 and 36 months. For the accelerated storage condition, testing for sterility and bacterial endotoxins is performed at release only. The stability specifications are listed below:

- TAMC: NMT 200 CFU/mL (as per USP <1111>)
- TYMC: NMT 20 CFU/mL (as per USP <1111>)

Post-Approval Stability Commitment (3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment.pdf)

The applicant, Pfizer Inc., provided a stability protocol and commitment. The applicant commits to perform annual post-approval stability studies on the first three commercial batches, then one commercial production batch of Xeljanz (Tofacitinib Oral Solution 1mg/mL, 240mL presentation).

**Assessment:**

**Adequate**

## P.8.3 STABILITY DATA

Stability data are provided through the 12-month (6-months for the accelerated storage condition) testing time point for Exhibit Batch No. K061818 stored in the long-term, intermediate and accelerated storage condition. Stability testing results of the Microbial Limits testing are provided and met the specifications.

**Assessment:**

**Adequate**

## 2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information
Post-dilution/reconstitution hold time

The is non-sterile drug product is intended for multiple-dose use. Storage instructions are as follows: store at 20-25°C, protected from light. After opening the contents should be used within 60 days. Antimicrobial effectiveness testing was performed as per USP <51> (please see Section P.2.5) to support the in-use period.

**Assessment:**

**Adequate**

## MICROBIOLOGY LIST OF DEFICIENCIES

***List of Deficiencies:*** There are no deficiencies to list at this time.

***Primary Microbiology Assessor Name and Date:*** Dionne Coker-Robinson, Ph.D. 06/24/2020

***Secondary Assessor Name and Date (and Secondary Summary, as needed):*** Yuansha Chen, Ph.D. 06/242020

Dionne Coker-Robinson

Digitally signed by Dionne Coker-Robinson
Date: 7/07/2020 03:13:29PM
GUID: 58921b8a0028500c9c6dfa8934d77256

Yuansha Chen

Digitally signed by Yuansha Chen
Date: 7/08/2020 10:28:47AM
GUID: 545289f5000727e1136ef94794e114b8

# CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

## 1.0 PRESCRIBING INFORMATION

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

The Prescribing Information is combined with the 5 mg immediate tablet and 11 mg extended release tablet and submitted in NDA 03214 supplement 26 dated 26-March-2020. The carton and container labels for the current oral solution dosage form are submitted in this NDA.

The labeling is deemed not ADEQUATE as proposed until it is revised satisfactorily to meet the regulatory requirements (See the **List of Deficiencies** at the end of this review).

## 1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use XELJANZ/XELJANZ XR/XELJANZ Oral Solution safely and effectively. See full prescribing information for XELJANZ/XELJANZ XR/XELJANZ Oral Solution.**

**XELJANZ® (tofacitinib) tablets, for oral use**
**XELJANZ® XR (tofacitinib) extended-release tablets, for oral use**
**XELJANZ® (tofacitinib) Oral Solution**
**Initial U.S. Approval: 2012**

**WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY AND THROMBOSIS**
*See full prescribing information for complete boxed warning.*

- **Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred. (5.1)**
- **If a serious infection develops, interrupt XELJANZ/XELJANZ XR/XELJANZ Oral Solution until the infection is controlled. (5.1)**
- **Prior to starting XELJANZ/XELJANZ XR/XELJANZ Oral Solution, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting XELJANZ/XELJANZ XR/XELJANZ Oral Solution. (5.1)**
- **Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)**
- **Thrombosis, including pulmonary embolism, deep venous thrombosis and arterial thrombosis have occurred in patients treated with XELJANZ and other Janus kinase inhibitors. Rheumatoid arthritis patients with at least one cardiovascular (CV) risk factor had a higher rate of all-cause mortality and thrombosis with XELJANZ 10 mg twice daily vs. 5 mg twice daily or TNF blockers. (5.2, 5.4)**
- **Lymphoma and other malignancies have been observed in patients treated with XELJANZ, including an increased rate of Epstein Barr Virus-associated post-transplant lymphoproliferative disorder. (5.3)**

## RECENT MAJOR CHANGES

| | |
|---|---|
| Boxed Warning | xx/2020 |
| Indications and Usage (1) | xx/2020 |
| Dosage and Administration (2.1) | xx/2020 |
| Dosage and Administration (2.2) | 12/2019 |
| Dosage and Administration (2.3) | 12/2019 |
| Dosage and Administration (2.4) | xx/2020 |
| Warnings and Precautions (5.1) | xx/2020 |
| Warnings and Precautions (5.2) | xx/2020 |
| Warnings and Precautions (5.3) | xx/2020 |
| Warnings and Precautions (5.4) | xx/2020 |
| Warnings and Precautions (5.5) | xx/2020 |
| Warnings and Precautions (5.7) | xx/2020 |
| Warnings and Precautions (5.8) | xx/2020 |

## INDICATIONS AND USAGE

XELJANZ/XELJANZ XR/XELJANZ Oral Solution is a Janus kinase (JAK) inhibitor indicated for:

- Rheumatoid Arthritis: XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. (b) (4) (b) (4)
  - *Limitations of Use:* Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1)
- Psoriatic Arthritis: XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs).
  - *Limitations of Use:* Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1)
- Ulcerative Colitis: XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response or who are intolerant to TNF blockers.
  - *Limitations of Use:* Use of XELJANZ/XELJANZ XR in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1)
- Polyarticular Course Juvenile Idiopathic Arthritis: XELJANZ/XELJANZ Oral Solution is indicated for the treatment of active polyarticular course juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older.
  - *Limitations of Use:* Use of XELJANZ/XELJANZ Oral Solution in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1)

## DOSAGE AND ADMINISTRATION

Administration Instructions

- Do not initiate XELJANZ/XELJANZ XR/XELJANZ Oral Solution if absolute lymphocyte count <500 cells/mm³, an absolute neutrophil count (ANC) <1000 cells/mm³ or hemoglobin <9 g/dL. (2.1)

Recommended Dosage

*Rheumatoid Arthritis*

- XELJANZ 5 mg twice daily or XELJANZ XR 11 mg once daily. (2.2)
- Recommended dosage in patients with moderate and severe renal impairment or moderate hepatic impairment is XELJANZ 5 mg once daily. (2, 8.7, 8.8)

*Psoriatic Arthritis (in combination with nonbiologic DMARDs)*

- XELJANZ 5 mg twice daily or XELJANZ XR 11 mg once daily. (2.2)
- Recommended dosage in patients with moderate and severe renal impairment or moderate hepatic impairment is XELJANZ 5 mg once daily. (2, 8.7, 8.8)

*Ulcerative Colitis*

- Induction: XELJANZ 10 mg twice daily or XELJANZ XR 22 mg once daily for 8 weeks; evaluate patients and transition to maintenance therapy depending on therapeutic response. If needed, continue XELJANZ 10 mg twice daily or XELJANZ XR 22 mg once daily for a maximum of 16 weeks. Discontinue XELJANZ 10 mg twice daily or XELJANZ XR 22 mg once daily after 16 weeks if adequate therapeutic response is not achieved. (2.3)
- Maintenance: XELJANZ 5 mg twice daily or XELJANZ XR 11 mg once daily. For patients with loss of response during maintenance treatment, XELJANZ 10 mg twice daily or XELJANZ XR 22 mg once daily may be considered and limited to the shortest duration, with careful consideration of the benefits and risks for the individual patient. Use the lowest effective dose needed to maintain response. (2.3)
- Dosage adjustment is needed in patients with moderate and severe renal impairment or moderate hepatic impairment: see full prescribing information. (2.3)

*Polyarticular Course Juvenile Idiopathic Arthritis*

- XELJANZ/XELJANZ Oral Solution 5 mg twice daily or weight-based equivalent twice daily (2.4).
- Dosage adjustment is needed in patients with moderate and severe renal impairment or moderate hepatic impairment: see full prescribing information. (2.4)

Dosage Adjustment

- See the full prescribing information for dosage adjustments by indication for patients receiving CYP2C19 and/or CYP3A4 inhibitors; in patients with moderate or severe renal impairment or moderate hepatic impairment; and patients with lymphopenia, neutropenia, or anemia. (2.2, 2.3, 2.4, 8.7, 8.8)
- Use of XELJANZ/XELJANZ XR/XELJANZ Oral Solution in patients with severe hepatic impairment is not recommended in any patient population. (2.2, 2.3, 2.4, 8.8)

## DOSAGE FORMS AND STRENGTHS

XELJANZ Tablets: 5 mg, 10 mg tofacitinib (3)
XELJANZ XR Tablets: 11 mg, 22 mg tofacitinib (3)
XELJANZ Oral Solution: 1 mg/mL tofacitinib (3)

## CONTRAINDICATIONS

None (4)

## WARNINGS AND PRECAUTIONS

- Serious Infections: Avoid use of XELJANZ/XELJANZ XR/XELJANZ Oral Solution during an active serious infection, including localized infections. (5.1)
- Thrombosis, including pulmonary, deep venous and arterial, some fatal: Reported more commonly in patients treated with XELJANZ 10 mg twice daily compared to 5 mg twice daily. Avoid XELJANZ/XELJANZ XR/XELJANZ Oral Solution in patients at risk. Promptly evaluate patients with symptoms of thrombosis and discontinue XELJANZ/XELJANZ XR/XELJANZ Oral Solution. (5.4)
- Gastrointestinal Perforations: Use with caution in patients that may be at increased risk. (5.5)

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **Product Title in Highlights** | | |
| Proprietary name | XELJANZ® | |
| Established name(s) | (tofacitinib) Oral Solution | Adequate |
| Route(s) of administration | Oral | Adequate |
| **Dosage Forms and Strengths Heading in Highlights** | | |
| Summary of the dosage form(s) and strength(s) in metric system. | 1 mg/mL tofacitinib | Adequate |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored" | N/A | |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package. | N/A | |

## 1.2 FULL PRESCRIBING INFORMATION

### 1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

> Administer XELJANZ Oral Solution using the included press-in bottle adapter and oral dosing syringe *[see Instructions for Use]*.

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **DOSAGE AND ADMINISTRATION section** | | |
| Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product) | Administer XELJANZ Oral Solution using the included press-in bottle adapter and oral dosing syringe *[see Instructions for Use]*. | **Adequate** |

### 1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

**3 DOSAGE FORMS AND STRENGTHS**

XELJANZ Tablets:

- 5 mg tofacitinib: White, round, immediate-release film-coated tablets, debossed with "Pfizer" on one side, and "JKI 5" on the other side.
- 10 mg tofacitinib: Blue, round, immediate-release film-coated tablets, debossed with "Pfizer" on one side, and "JKI 10" on the other side.

XELJANZ XR Tablets:

- 11 mg tofacitinib: Pink, oval, extended-release film-coated tablets with a drilled hole at one end of the tablet band and "JKI 11" printed on one side of the tablet.
- 22 mg tofacitinib: Beige, oval, extended-release film-coated tablets with a drilled hole at one end of the tablet band and "JKI 22" printed on one side of the tablet.

XELJANZ Oral Solution:
1 mg/mL tofacitinib: Clear, colorless oral solution.

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **DOSAGE FORMS AND STRENGTHS section** | | |
| Available dosage form(s) | Oral solution | **Adequate** |
| Strength(s) in metric system | 1mg/mL | **Adequate** |
| If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance | Provided in section 11 | |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting | clear colorless oral solution | **Adequate** |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored" | N/A | |
| For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package. | N/A | |

### 1.2.3 Section 11 (DESCRIPTION)

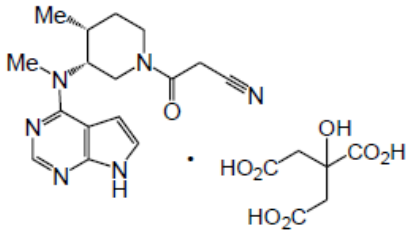
## 11 DESCRIPTION

XELJANZ/XELJANZ XR (tofacitinib) tablets and XELJANZ (tofacitinib) Oral Solution are formulated with the citrate salt of tofacitinib, a JAK inhibitor.

Tofacitinib citrate is a white to off-white powder with the following chemical name: (3R,4R)-4-methyl-3-(methyl-7H-pyrrolo [2,3-d]pyrimidin-4-ylamino)-ß-oxo-1-piperidinepropanenitrile, 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

The solubility of tofacitinib citrate in water is 2.9 mg/mL.

Tofacitinib citrate has a molecular weight of 504.5 Daltons (or 312.4 Daltons as the tofacitinib free base) and a molecular formula of $C_{16}H_{20}N_6O \cdot C_6H_8O_7$. The chemical structure of tofacitinib citrate is:




XELJANZ is supplied for oral administration as a 5 mg white round, immediate-release film-coated tablet. Each tablet of XELJANZ contains 5 mg tofacitinib (equivalent to 8.08 mg tofacitinib citrate) and the following inactive ingredients: croscarmellose sodium, HPMC

2910/Hypromellose 6cP, lactose monohydrate, macrogol/PEG3350, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin.

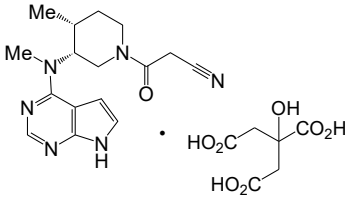
XELJANZ is supplied for oral administration as a 10 mg blue round, immediate-release film-coated tablet. Each 10 mg tablet of XELJANZ contains 10 mg tofacitinib (equivalent to 16.16 mg of tofacitinib citrate) and the following inactive ingredients: croscarmellose sodium, FD&C Blue #1/Brilliant Blue FCF Aluminum Lake, FD&C Blue #2/Indigo Carmine Aluminum Lake, HPMC 2910/Hypromellose 6cP, lactose monohydrate, macrogol/PEG3350, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin.

XELJANZ XR is supplied for oral administration as a 11 mg pink, oval, extended-release film-coated tablet with a drilled hole at one end of the tablet band. Each 11 mg tablet of XELJANZ XR contains 11 mg tofacitinib (equivalent to 17.77 mg tofacitinib citrate) and the following inactive ingredients: cellulose acetate, copovidone, hydroxyethyl cellulose, hydroxypropyl cellulose, HPMC 2910/Hypromellose, magnesium stearate, red iron oxide, sorbitol, titanium dioxide and triacetin. Printing ink contains, ammonium hydroxide, ferrosoferric oxide/black iron oxide, propylene glycol, and shellac glaze.

XELJANZ XR is supplied for oral administration as a 22 mg beige, oval, extended-release film-coated tablet with a drilled hole at one end of the tablet band. Each 22 mg tablet of XELJANZ XR contains 22 mg tofacitinib (equivalent to 35.54 mg tofacitinib citrate) and the following inactive ingredients: cellulose acetate, copovidone, FD&C Blue #2 Aluminum Lake, hydroxyethyl cellulose, hydroxypropyl cellulose, HPMC 2910/Hypromellose, magnesium stearate, red iron oxide, sorbitol, titanium dioxide, triacetin, and yellow iron oxide. Printing ink contains ammonium hydroxide, ferrosoferric oxide/black iron oxide, propylene glycol, and shellac glaze.

XELJANZ Oral Solution is supplied for oral administration as a 1 mg/mL clear, colorless solution. Each 1 mL of XELJANZ Oral Solution contains 1 mg of tofacitinib (equivalent to 1.62 mg/ml tofacitinib citrate) and the following inactive ingredients: grape flavor (natural), hydrochloric acid, lactic acid, purified water, sodium benzoate, sucralose, and xylitol.

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **DESCRIPTION section** | | |
| Proprietary and established name(s) | XELJANZ Oral Solution | **Adequate** |
| Dosage form(s) and route(s) of administration | oral solution | **Adequate** |
| If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance. | Each 1 mL of XELJANZ Oral Solution contains 1 mg of tofacitinib (equivalent to 1.62 mg/ml tofacitinib citrate) | **Adequate** |
| List names of all inactive ingredients. Use USP/NF names. Avoid Brand names. | grape flavor (natural), hydrochloric acid, lactic acid, purified water, sodium benzoate, sucralose, and xylitol | **Adequate** |
| For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. | N/A | |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol | N/A | |
| Statement of being sterile (if applicable) | N/A | |
| Pharmacological/ therapeutic class | JAK inhibitor | **Adequate** |

| | | |
|---|---|---|
| Chemical name, structural formula, molecular weight | Chemical name: (3R,4R)-4-methyl-3-(methyl-7H-pyrrolo [2,3-d]pyrimidin-4-ylamino)-ß-oxo-1-piperidinepropanenitrile, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)<br>Molecular formula: $C_{16}H_{20}N_6O \cdot C_6H_8O_7$<br>molecular weight: 312.4 g/mol (free base); 504.5 g/mol (salt)<br>  | **Adequate** |
| If radioactive, statement of important nuclear characteristics. | N/A | |
| Other important chemical or physical properties (such as pKa or pH) | Tofacitinib citrate is a white to off-white powder. The solubility of tofacitinib citrate in water is 2.9 mg/mL | **Adequate** |

**Section 11 (DESCRIPTION) Continued**

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| For oral prescription drug products, include gluten statement if applicable | N/A | |
| Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity" | N/A | |

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

How supplied information for XELJANZ Oral Solution is shown in Table 22.

**Table 22: How Supplied Information for XELJANZ Oral Solution**

| | **Bottle Fill (volume mL)** | **NDC Number** |
|---|---|---|
| **XELJANZ Oral Solution 1 mg/mL tofacitinib oral solution** Clear, colorless solution | 240 mL | NDC 0069-1029-02 |

XELJANZ Oral Solution

XELJANZ 1 mg/ mL oral solution is a clear, colorless solution that contains 1 mg of tofacitinib. It is packaged in HDPE bottles as follows:

Each bottle is packaged with one press-in bottle adapter and one 5 mL oral dosing syringe with 3.2 mL, 4 mL, and 5 mL gradations. The press-in bottle adapter and oral dosing syringe are not made with natural rubber latex.

Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F). [See USP Controlled Room Temperature].

Store in the original bottle and carton to protect from light.

Use contents of bottle within 60 days of opening.

Discard remaining oral solution after 60 days.

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **HOW SUPPLIED/STORAGE AND HANDLING section** | | |
| Available dosage form(s) | Oral solution | **Adequate** |
| Strength(s) in metric system | 1 mg/mL | **Adequate** |
| Available units (e.g., bottles of 100 tablets) | 240 mL | **Adequate** |
| Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number | Clear colorless solution<br>NDC 0069-1029-02 | **Adequate** |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored" | N/A | |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package. | N/A | |
| Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.) | Store in the original bottle and carton to protect from light.<br>Use contents of bottle within 60 days of opening. Discard remaining oral solution after 60 days. | **Adequate** |
| If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat." | N/A | |
| Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. | Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F). [See USP Controlled Room Temperature]. | **Adequate** |

| | | |
|---|---|---|
| Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free." | The press-in bottle adapter and oral dosing syringe are not made with natural rubber latex. | **Adequate** |
| Include information about child-resistant packaging | N/A | |

### 1.2.5 Other Sections of Labeling

N/A

### *1.2.6* Manufacturing Information After Section 17 (for drug products)

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **Manufacturing Information After Section 17** | | |
| Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer | Distributed by Pfizer Labs Division of Pfizer Inc, NY, NY 10017<br>LAB-0445-19.1 | Adequate |

## 2.0 PATIENT LABELING

**I. The following CMC information is provided in the Medication Guide (tablets, extended-release tablets and oral solution) and is adequate**

**How should I store XELJANZ/XELJANZ XR/XELJANZ Oral Solution?**

- **Store XELJANZ/XELJANZ XR at room temperature between 68°F to 77°F (20°C to 25°C).**
- **Store XELJANZ Oral Solution at room temperature between 68°F to 77°F (20°C to 25°C) in original bottle and carton to protect from light.** (b) (4) (b) (4)
- **Safely throw away medicine that is out of date or no longer needed. Discard remaining oral solution after 60 days.**

**Keep XELJANZ/XELJANZ XR/XELJANZ Oral Solution and all medicines out of the reach of children.**

**What are the ingredients in XELJANZ Oral Solution?**
**Active ingredient: tofacitinib citrate**

**Inactive ingredients: grape flavor (natural), hydrochloric acid, lactic acid, purified water, sodium benzoate, sucralose, and xylitol.**

**II. The following CMC information is provided in the Instruction for Use (oral solution) and is adequate**

- **Important information about measuring XELJANZ oral solution**

**Always use the oral dosing syringe that comes with your XELJANZ oral solution to measure and (b) (4) your prescribed dose. Ask your healthcare provider or pharmacist to show you how to measure your prescribed dose if you are not sure.**

- **How should I store XELJANZ?**

**Store XELJANZ oral solution at room temperature between 20°C to 25°C (68°F to 77°F), (b) (4)**
**Always store XELJANZ in its original bottle and carton (b) (4) to protect from light.**
**Keep XELJANZ and all medicines out of the reach of children.**

**Use (b) (4) within 60 days of opening.**
**Discard remaining XELJANZ oral solution after 60 days.**
**To help you remember when to (b) (4) your XELJANZ bottle you can write the date of first**
**use on the carton and below:**
**Date of first use ____ / ____ / ____.**
**Before each use:**
**Wash your hands with soap and water and place the items from the carton on a clean flat surface.**

- **Detailed graphic instruction (not copied here) for the measurement of oral solution using co-packaged syringe is provided and acceptable from CMC perspective**

## 3.0 CARTON AND CONTAINER LABELING

## 3.1 Container Label

3 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

| Item | Information Provided in the NDA | Assessor's Comments about Carton Labeling |
|---|---|---|
| Proprietary name, established name, and dosage form (font size and prominence | Xeljanz (tofacitinib) oral solution | **Adequate** |
| Dosage strength | 1 mg/mL | **Adequate** |
| Route of administration | oral | **Adequate** |
| If the active ingredient is a salt, include the equivalency statement per FDA Guidance | Not provided | **Not Adequate**<br>• Include an equivalence statement that Each 1 mL of oral solution contains 1 mg of tofacitinib (equivalent to 1.62 mg tofacitinib citrate) |
| Net contents (e.g. tablet count) | 240 mL | **Adequate** |
| "Rx only" displayed on the principal display | Provided | **Adequate** |
| NDC number | Provided | **Adequate** |
| Lot number and expiration date | Provided | **Adequate** |
| Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD. | **Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F).** [See USP Controlled Room Temperature].<br>**STORE IN ORIGINAL BOTTLE AND CARTON TO PROTECT FROM LIGHT.**<br>**Do not use if tamper evident seal is broken or missing.**<br>The oral dosing syringe and adapter are not made with natural rubber latex. (b) (4)<br>See prescribing information (b) (4) (b) (4)<br>See Instructions for Use for correct use of the oral dosing syringe.<br>Each mL of oral solution contains 1mg of tofacitinb.<br>**Use contents of bottle within 60 days of opening.**<br>**Discard remaining oral solution after 60 days.**<br>**Date of first use ____ / ____ / ____.** | **Adequate** |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use) | N/A | **Adequate** |

| | | |
|---|---|---|
| Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement. | N/A | |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol | N/A | |
| Bar code | Provided | **Adequate** |

| Item | Information Provided in the NDA | Assessor's Comments about Carton Labeling |
|---|---|---|
| Name of manufacturer/distributor | Provided | **Adequate** |
| Medication Guide (if applicable) | Provided | **Adequate** |
| No text on Ferrule and Cap overseal | N/A | |
| When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label. | N/A | |
| And others, if space is available | Contents in the carton is provided below:<br>Contents:<br>• Oral solution bottle<br>• 1 Oral dosing syringe<br>• 1 Press-in bottle adapter<br>• Prescribing Information<br>• Medication Guide<br>• Instructions for Use | **Adequate** |

**Assessment of Carton and Container Labeling: *Inadequate***

Include an equivalence statement that Each mL of oral solution contains 1 mg of tofacitinib (equivalent to 1.62 mg tofacitinib citrate)

## ITEMS FOR ADDITIONAL ASSESSMENT

### List of Deficiencies

**A. For Container/Carton Labels:**

- Include an equivalence statement that Each  mL of oral solution contains 1 mg of tofacitinib (equivalent to 1.62 mg tofacitinib citrate)

### *Overall Assessment and Recommendation:*

The NDA is not ready for approval in its present form per CFR 314.125(b)(6) until the outstanding labeling issues listed in the **List of Deficiencies** are satisfactorily resolved.

*Primary Labeling Assessor Name and Date:*

***Zhengfang Ge, Ph. D.***
*Reviewer, BRANCH IV/DIVISION II*
*OFFICE OF NEW DRUG PRODUCT*

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

***Wendy Wilson, Ph. D.***
*Director/DIVISION II*
*OFFICE OF NEW DRUG PRODUCT*

Zhengfang Ge

Digitally signed by Zhengfang Ge
Date: 7/21/2020 01:22:44PM
GUID: 508da7210002a030e76df4f60ccd142a

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 7/21/2020 02:13:10PM
GUID: 50816dbc000085595ca3284bbca465a8

Craig Bertha

Digitally signed by Craig Bertha
Date: 8/12/2020 01:42:23PM
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**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.**

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/s/

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CRAIG M BERTHA
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