CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761275Orig1s000

OTHER REVIEW(S)

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

PATIENT LABELING REVIEW

Date:	February 9, 2024
To:	Susie Choi 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)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN 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 (IFUs)
Drug Name (nonproprietary name):	[MSB11456] TYENNE (tocilizumab-aazg)[1]
Dosage Form and Route:	injection, for intravenous or subcutaneous use
Application Type/Number:	BLA 761275
Applicant:	Fresenius Kabi USA, LLC

[1] MSB11456 has been developed as a proposed biosimilar to US-licensed Actemra (tocilizumab). The proposed proprietary name Tyenne was found conditionally acceptable on November 30, 2022. The nonproprietary name "tocilizumab-aazg" was found conditionally acceptable on March 2, 2023.

1 INTRODUCTION

On September 5, 2023, Fresenius Kabi USA, LLC submitted for the Agency's review a Complete Response to the Agency's Complete Response Letter issued on May 31, 2023, for their original Biologics License Application (BLA) 761275 for TYENNE (tocilizumab-aazg) injection, a proposed biosimilar to US-licensed ACTEMRA (tocilizumab) injection.

The Applicant proposes TYENNE (tocilizumab-aazg) injection, for subcutaneous use to be licensed for the same indications as the single reference product ACTEMRA (with the exception of those indications under orphan drug exclusivity), for the treatment of the following:

- **Rheumatoid Arthritis (RA):** Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
- **Giant Cell Arteritis (GCA):** Adult patients with giant cell arteritis.
- **Polyarticular Juvenile Idiopathic Arthritis (PJIA):** Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.
- **Systemic Juvenile Idiopathic Arthritis (SJIA):** Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

This collaborative 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 October 17, 2023 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for TYENNE (tocilizumab-aazg) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft TYENNE (tocilizumab-aazg) MG and IFUs received on September 5, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 18, 2024.
- Draft TYENNE (tocilizumab-aazg) Prescribing Information (PI) received on September 5, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 18, 2024.
- Approved ACTEMRA (tocilizumab) comparator labeling dated December 21, 2022.

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 APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFUs we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFUs 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 IFUs meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFUs are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFUs are 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 IFUs.

Please let us know if you have any questions.

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/

MARY E CARROLL
02/09/2024 09:58:59 AM

KYLE SNYDER
02/09/2024 10:38:53 AM

MARCIA B WILLIAMS
02/09/2024 10:45:13 AM

LASHAWN M GRIFFITHS
02/09/2024 11:41:35 AM

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

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

Memorandum

Date: January 19, 2024

To: Susie Choi, Senior Regulatory Project Manager
Division of Rheumatology and Transplant Medicine

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

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for TYENNE® (tocilizumab-aazg) injection, for subcutaneous use

BLA: 761275

Background:

In response to DRTM's consult request dated November 14, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and Instructions for Use (IFU) for the original BLA submission for TYENNE® (tocilizumab-aazg) injection, for subcutaneous use.

PI/Medication Guide/IFU:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on January 17, 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.

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

48 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

KYLE SNYDER
01/19/2024 03:32:51 PM

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:	December 11, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761275
Product Name, Dosage Form, and Strength:	Tyenne (tocilizumab-aazg) injection, 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400mg/20 mL (20 mg/mL) in single-dose vials; 162 mg/0.9 mL prefilled syringe or autoinjector
Applicant/Sponsor Name:	Fresenius Kabi
TTT ID #:	2023-2098-6
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised blister label and carton labeling received on November 29, 2023 for Tyenne. The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container label and carton labeling for Tyenne (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that OBP made.[a]

2 CONCLUSION

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

[a] Choi, S. Information Request for Tyenne (BLA 761275). Silver Spring (MD): FDA, CDER, OSE, OND/DRTM (US); 2023 NOV 15. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80708ea3.

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/s/

SARAH K VEE
12/11/2023 10:05:40 AM

DAMON A BIRKEMEIER
12/11/2023 10:30:33 AM

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:	November 1, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761275
Product Name, Dosage Form, and Strength:	Tyenne (tocilizumab-aazg) injection, 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) in single-dose vials; 162 mg/0.9 mL prefilled syringe or autoinjector
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Fresenius Kabi
FDA Received Date:	September 5, 2023
TTT ID #:	2022-2098-5
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Tyenne (tocilizumab-aazg) injection, the Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the proposed Tyenne prescribing information, container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTROY

BLA 761275 was originally submitted on May 30, 2022. However, the application received a complete response (CR) on May 31, 2023. Thus, Fresenius Kabi submitted a response to the CR on September 5, 2023. We note that the prescribing information, container label, and carton labeling were reviewed in the previous review cycle (see Appendix B).

3 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
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

4 CONCLUSION & RECOMMENDATIONS

We reviewed the proposed prescribing information, Medication Guide, and Instructions for Use and did not identify areas of vulnerability that may lead to medication error. We 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.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tyenne received on September 5, 2023 from Fresenius Kabi, and the listed drug (LD).

Table 2. Relevant Product Information for Tyenne and the Listed Drug		
Product Name	Tyenne	Actemra[a]
Initial Approval Date	N/A	1/08/2010
Nonproprietary Name	tocilizumab-aazg	tocilizumab

[a] Actemra [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. DEC 2022. [cited 2023 OCT 19]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125472s049lbl.pdf.

Table 2. Relevant Product Information for Tyenne and the Listed Drug		
Product Name	Tyenne	Actemra[a]
Indication	Rheumatoid Arthritis (RA) - Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs). Giant Cell Arteritis (GCA) - Adult patients with giant cell arteritis. Polyarticular Juvenile Idiopathic Arthritis (PJIA) - Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis (SJIA) - Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.	Rheumatoid Arthritis (RA) • Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs). Giant Cell Arteritis (GCA) • Adult patients with giant cell arteritis. Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD) • Slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) Polyarticular Juvenile Idiopathic Arthritis (PJIA) • Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis (SJIA) • Patients 2 years of age and older with active systemic juvenile idiopathic arthritis. Cytokine Release Syndrome (CRS) • Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome. Coronavirus Disease 2019 (COVID-19) • Hospitalized adult patients with coronavirus disease 2019 (COVID-

Table 2. Relevant Product Information for Tyenne and the Listed Drug		
Product Name	Tyenne	Actemra[a]
		19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).
Route of Administration	injection Intravenous or subcutaneous Injection	
Dosage Form	injection	injection
Strength	80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) in single-dose vials; 162 mg/0.9 mL prefilled syringe or autoinjector	80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) in single-dose vials; 162 mg/0.9 mL in prefilled syringe or ACTPen® autoinjector

<table>
<tr><th colspan="3">Table 2. Relevant Product Information for Tyenne and the Listed Drug</th></tr>
<tr><th>Product Name</th><th>Tyenne</th><th>Actemra[a]</th></tr>
<tr><td>Dose and Frequency</td><td>
Rheumatoid Arthritis
Recommended Adult Intravenous Dosage:
When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.

Recommended Adult Subcutaneous Dosage:
<table>
<tr><td>Patients less than 100 kg weight</td><td>162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response</td></tr>
<tr><td>Patients at or above 100 kg weight</td><td>162 mg administered subcutaneously every week</td></tr>
</table>

Giant Cell Arteritis

Recommended Adult Intravenous Dosage:
The recommended dose is 6 mg per kg every 4 weeks in combination with a tapering course of glucocorticoids. TYENNE can be used alone following discontinuation of glucocorticoids.

Recommended Adult Subcutaneous Dosage:
The recommended dose is 162 mg given once every week as a subcutaneous injection, in combination with a tapering course of glucocorticoids.

A dose of 162 mg given once every other week as a subcutaneous injection, in combination with a tapering course of glucocorticoids, may be prescribed based on clinical considerations.

TYENNE can be used alone following discontinuation of glucocorticoids.

Polyarticular Juvenile Idiopathic Arthritis
<table>
<tr><td colspan="2">Recommended Intravenous PJIA Dosage Every 4 Weeks</td></tr>
<tr><td>Patients less than 30 kg weight</td><td>10 mg per kg</td></tr>
<tr><td>Patients at or above 30 kg weight</td><td>8 mg per kg</td></tr>
</table>
<table>
<tr><td colspan="2">Recommended Subcutaneous PJIA Dosage</td></tr>
<tr><td>Patients less than 30 kg weight</td><td>162 mg once every three weeks</td></tr>
</table>
</td><td>
Rheumatoid Arthritis
Recommended Adult Intravenous Dosage:
When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.

Recommended Adult Subcutaneous Dosage:
<table>
<tr><td>Patients less than 100 kg weight</td><td>162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response</td></tr>
<tr><td>Patients at or above 100 kg weight</td><td>162 mg administered subcutaneously every week</td></tr>
</table>

Giant Cell Arteritis

Recommended Adult Intravenous Dosage:
The recommended dose is 6 mg per kg every 4 weeks in combination with a tapering course of glucocorticoids. TYENNE can be used alone following discontinuation of glucocorticoids.

Recommended Adult Subcutaneous Dosage:
The recommended dose is 162 mg given once every week as a subcutaneous injection, in combination with a tapering course of glucocorticoids.

A dose of 162 mg given once every other week as a subcutaneous injection, in combination with a tapering course of glucocorticoids, may be prescribed based on clinical considerations.

ACTEMRA can be used alone following discontinuation of glucocorticoids.

Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)
Recommended Adult Subcutaneous Dosage:
The recommended dose of ACTEMRA for adult patients with SSc-ILD is 162 mg given once every week as a subcutaneous injection.

Polyarticular Juvenile Idiopathic Arthritis
<table>
<tr><td colspan="2">Recommended Intravenous PJIA Dosage Every 4 Weeks</td></tr>
<tr><td>Patients less than 30 kg weight</td><td>10 mg per kg</td></tr>
<tr><td>Patients at or above 30 kg weight</td><td>8 mg per kg</td></tr>
</table>
</td></tr>
</table>

Table 2. Relevant Product Information for Tyenne and the Listed Drug

Product Name	Tyenne	Actemra[a]

Tyenne

Patients at or above 30 kg weight	162 mg once every two weeks

Systemic Juvenile Idiopathic Arthritis

Recommended Intravenous SJIA Dosage Every 2 Weeks	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Recommended Subcutaneous SJIA Dosage	
Patients less than 30 kg weight	162 mg every two weeks
Patients at or above 30 kg weight	162 mg every week

Actemra[a]

Recommended Subcutaneous PJIA Dosage	
Patients less than 30 kg weight	162 mg once every three weeks
Patients at or above 30 kg weight	162 mg once every two weeks

Systemic Juvenile Idiopathic Arthritis

Recommended Intravenous SJIA Dosage Every 2 Weeks	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Recommended Subcutaneous SJIA Dosage	
Patients less than 30 kg weight	162 mg every two weeks
Patients at or above 30 kg weight	162 mg every week

Cytokine Release Syndrome (2.7)

Recommended Intravenous CRS Dosage	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg
Alone or in combination with corticosteroids.	

Coronavirus Disease 2019

The recommended dosage of ACTEMRA for adult patients with COVID-19 is 8 mg per kg administered by a 60-minute intravenous infusion.

How Supplied	Carton of 1 single dose vial Carton of 1 prefilled syringe Carton of 1 autoinjector	Carton of 1 single dose vial Carton of 1 prefilled syringe Carton of 1 ACTPen autoinjector

Table 2. Relevant Product Information for Tyenne and the Listed Drug		
Product Name	Tyenne	Actemra[a]
Storage	Do not use beyond expiration date on the container, package, prefilled syringe, or autoinjector. TYENNE must be refrigerated at 36°F to 46°F (2ºC to 8ºC). Do not freeze. A single prefilled syringe (or autoinjector) may be stored at (b) (4) 77°F (25°C) for a single period of up to 14 days. (b) (4) Protect the vials, syringes, and autoinjectors from light by storage in the original package until time of use, and keep syringes and autoinjectors dry.	Do not use beyond expiration date on the container, package, prefilled syringe, or autoinjector. ACTEMRA must be refrigerated at 36°F to 46°F (2ºC to 8ºC). Do not freeze. Protect the vials, syringes, and autoinjectors from light by storage in the original package until time of use, and keep syringes and autoinjectors dry. Once removed from the refrigerator, the prefilled syringe and autoinjector can be stored up to 2 weeks at or below 86°F (30°C). The prefilled syringe and autoinjector must always be kept in the carton.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 19, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, “Tyenne”. Our search identified five previous reviews and we confirmed that our previous recommendations were implemented.

McMillan, T. Label and Labeling Review for Tyenne (BLA 761275). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 DEC 15. TTT ID No.: 2022-2098.

McMillan, T. Label and Labeling Review for Tyenne (BLA 761275). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JAN 19. TTT ID No.: 2022-2098-1.

McMillan, T. Label and Labeling Review for Tyenne (BLA 761275). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 FEB 18. TTT ID No.: 2022-2098-2.

McMillan, T. Label and Labeling Review for Tyenne (BLA 761275). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 MAR 30. TTT ID No.: 2022-2098-3.

McMillan, T. Label and Labeling Review for Tyenne (BLA 761275). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 APR 13. TTT ID No.: 2022-2098-4.

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,[b] along with postmarket medication error data, we reviewed the following Tyenne labels and labeling submitted by Fresenius Kabi.

- Container label received on March 21, 2023 and April 6, 2023
- Carton labeling received on March 21, 2023 and April 6, 2023
- Instructions for Use received on April 14, 2023 and October 12, 2022, available from
  AI: \\CDSESUB1\evsprod\BLA761275\0039\m1\us\114-labeling\114a-draft-label
  PFS: \\CDSESUB1\evsprod\BLA761275\0010\m1\us\114-labeling\114a-draft-label

- Prescribing Information (Image not shown) received on March 21, 2023, available from \\CDSESUB1\evsprod\BLA761275\0032\m1\us\114-labeling\114a-draft-label

- Medication Guide received on March 21, 2023, available from \\CDSESUB1\evsprod\BLA761275\0032\m1\us\114-labeling\114a-draft-label

F.2 Label and Labeling Images

Container label(s)

(b) (4)

[redacted]

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

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/s/

SARAH K VEE
11/01/2023 11:19:23 AM

IDALIA E RYCHLIK
11/01/2023 04:04:42 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	3/7/2023		
To:	Anita Brown		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	CDER/OPQ/OPRO/DRBPMI/RBPMB1
From	Kathleen Fitzgerald OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Division Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA 761275, MSB11456 (tocilizumab) ICC2200610 ICCR 00858362		
Recommendation	**Filing Recommendation Date:** Click or tap to enter a date. ☐ CDRH did not provide a Filing Recommendation ☑ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: 10/27/2022 ☐ CDRH did not provide a Mid-Cycle Recommendation ☑ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 2/28/2023 ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Kathleen E. Fitzgerald -S Digitally signed by Kathleen E. Fitzgerald -S Date: 2023.03.08 09:18:54 -05'00'	Courtney Evans -S Digitally signed by Courtney Evans -S Date: 2023.03.14 13:36:44 -04'00'	

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761275
Sponsor	Fresenius Kabi USA, LLC
Drug/Biologic	MSB11456 (tocilizumab)
Indications for Use	Rheumatoid Arthritis: Adult patients with modrately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs
Device Constituent	Pre-Filled Syringe and Autoinjector
Related Files	None

Review Team		
Lead Device Reviewer	*Kathleen Fitzgerald*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
None		

Important Dates	
Discipline-Specific Review Memos Due	N/A
Final Lead Device Review Memo Due	January 23, 2022
Interim Due Dates	**Meeting/Due Date**
Filing	
74-Day Letter	
Mid-Cycle	October 27, 2022
Primary Review	January 23, 2022
Internal Meeting(s)	
Sponsor Meeting(s)	

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	
Clinical Validation			X	
Human Factors Validation			X	Reviewed by DMEPA
Facilities & Quality Systems	X			

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

TABLE OF CONTENTS

3. PURPOSE/BACKGROUND

3.1. Scope

Fresenius Kabi USA, LLC is requesting approval of MSB11456 (tocilizumab). The device constituent of the combination product is a Pre-Filled Syringe and Autoinjector.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

Autoinjector and safety device on the PFS

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Autoinjector and safety device on the PFS

This review will not cover the following review areas:

No drug contacting components. Will not review Primary container closer such as PFS or vial. Human factors reviewed by DMEPA.

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

None

3.2.1. Related Files

3.3. Indications for Use

Combination Product	Indications for Use
MSB11456 (tocilizumab)	Rheumatoid Arthritis: Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs
Auto-Injector and PFS with safety device	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
PFS with safety device	3.2.R2.1

EDR: \\CDSESUB1\evsprod\BLA761275\0001

Cover Letter: \\CDSESUB1\evsprod\BLA761275\0001\m1\us\12-cover-letter\cover-letter.pdf

4. DEVICE DESCRIPTION

4.1. Device Description

Letter of Authorization locations and device DMFs and MAFs.

MAF/DMF/510(k) Number	Applicant	Component Description	Related Presentation	Location
(b) (4)		8 mL Vial	• 80 mg/4 mL Vial presentation	Refer to 1.4.2 LOA_(b) (4)_8 mL Vial
		20 mL Vial	• 200 mg/10 mL Vial • 400 mg/20 mL Vial	Refer to 1.4.2 LOA_(b) (4)_20 mL Vial
		Vial Stopper	• 80 mg/4 mL Vial • 200 mg/10 mL Vial • 400 mg/20 mL Vial	Refer to 1.4.2 LOA_(b) (4)-stopper
		Vial Stopper	• 80 mg/4 mL Vial • 200 mg/10 mL Vial • 400 mg/20 mL Vial	Refer to 1.4.2 LOA_(b) (4)-stopper
		Syringe	• PFS(b) (4) and auto-injector	Refer to 1.4.2 LOA_(b) (4)_Syringe_(b) (4)
		Plunger stopper	• PFS (b) (4)	Refer to 1.4.2 LOA_(b) (4)Plunger stopper
	(b) (4) autoinjector		• Auto-injector	Refer to 1.4.2_LOA_(b) (4) autoinjector
	(b) (4) safety device (1 mL Cut Flange / Round Flange)		• PFS(b) (4)	Refer to 1.4.2 LOA_(b) (4)

Prefilled Syringe:

The MSB11456 drug product (DP) is a sterile, preservative-free solution for injection intended for subcutaneous administration. The MSB11456 Prefilled Syringe with Safety System (PFS (b) (4): Prefilled Syringe with (b) (4)) is a disposable, single-use, fixed dose (162 mg/0.9 mL), prefilled, and ready-to-use combination product.
The prefilled primary container ((b) (4) 1 mL syringe with 27G, ½-inch staked needle with rigid needle shield and plunger stopper). The primary container is presented in section 3.2.P.7.P (refer to 3.2.P.7.P - Container Closure System) • an anti-needlestick passive safety system, off-the-shelf (b) (4)® device platform from (b) (4), (b) (4) composed of: a safety device, a plunger rod attached to the primary container and an extended finger flange with elements.

Drawing of the MSB11456 PFS (b) (4) Before and After Use

The safety system is composed of the 3 following components: • the Safety device, • the Plunger Rod, • the Extended Finger Flange.

Figure 3 [(b) (4)] **Safety Device, Plunger Rod and Extended Finger Flan**

Table 3 **PFS** [(b) (4)] **Device Assembly Components**

Component	Manufacturer / Description or materials
Safety system	Manufacturer: [(b) (4)] Product description: [(b) (4)] 1mL Staked Safety System Material: [(b) (4)] and stainless steel
Plunger Rod	Manufacturer: [(b) (4)] Product description: [(b) (4)] or 1mL Long Plunger Rod Material: [(b) (4)] – Orange
Extended Finger Flange	Manufacturer: [(b) (4)] Product description: [(b) (4)] for 1mL Long Finger Flange Material: [(b) (4)] – Orange

Table 2 Applicable Standards to the Development of the PFS (b) (4)

Standard Reference	Standard Title
ISO 11608-1:2014	Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems
ISO 11608-3: 2012	Needle-based injection systems for medical use – Requirements and test methods Part 3: Finished containers
ISO 23908:2011	Sharps Injury Protection – Requirements and test methods – Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling
Guidance for Industry and FDA Staff	Medical Devices with Sharps Injury Prevention Features
ISO 10993-1: 2018	Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process
ASTM D4169 – 16	Standard Practice for Performance Testing of Shipping Containers and Systems
ASTM F1980 - 16	Accelerated Aging testing
FDA Guidance	"Applying Human Factors and Usability Engineering to Medical Devices Guidance for Industry and Food and Drug Administration Staff", issued Feb. 3, 2016
IEC 62366-1: 2015 + AMD1:2020	Medical devices - Application of usability engineering to medical devices

4.2. Steps for Using the Device

Table 1 Use Steps of the MSB11456 PFS (b) (4)

Use steps	Use steps illustration	Use steps short description
a	(b) (4)	User removes the protective cap (Rigid Needle Shield)
b		User pinches the skin and inserts the needle as far as it will go into the pinched skin with a quick, short movement. User holds the PFS like a pencil while doing this.
c		Injection: The user slowly presses down the plunger rod with the thumb. This results in the injection of the drug. As soon as the plunger rod is fully pressed down, the (b) (4) system is activated.
d		Removal of (b) (4) from the skin: Activation of the (b) (4) System causes a spring to push up the plunger rod including the PFS. This removes the needle from the skin. When it reaches the top, the needle is getting out of the skin and the PFS (b) (4) is in a locked position. This protects against needlestick injuries. Once the PFS (b) (4) is in locked mode, it can no longer be used.
e		Disposal of the (b) (4) After use, the device is discarded in a sharps disposal container.

(b) (4) Autoinjector:

The MSB11456 Auto-injector (AI) is a disposable, single-use, fixed dose (162 mg/0.9 mL), prefilled, and ready-to-use combination product. It is composed of:

- a prefilled primary container Refer to section 3.2.P.7 - Container Closure System (PFS).
- an auto-injector ((b) (4)) based on a platform device developed by (b) (4).

The design features of the (b) (4) auto-injector include:

- Push-on-skin injection release
- Single step activation with automatic needle shielding after injection
- Cap for easy removal of the rigid needle shield (RNS)
- (b) (4) elements and non-rolling shape for improved ergonomics.

The MSB11456 AI has two main parts the user will interact with during use:

- the cap,
- the body of the AI.

The AI has a passive anti-needlestick system composed of a needle cover (integral to the body) that automatically covers the needle and locks in extended position after injection is performed and needle is removed from skin. The AI from (b) (4) is represented in Figure 1 and Figure 2 below with its key components identified.

Figure 1 (b) (4) Auto-injector

(b) (4)

Figure 2 (b) (4) Auto-injector (uncapped) Main External Elements

(b) (4)

Applicable standards for autoinjector:

Standard Reference	Standard Title
ISO 11608-1: 2014	Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems
ISO 11608-3: 2012	Needle-based injection systems for medical use - Requirements and test methods Part 3: Finished containers
ISO 11608-5: 2012	Needle-based injection systems for medical use - Requirements and test methods Part 5: Automated Functions
ISO 23908: 2011	Sharps Injury Protection – Requirements and test methods – Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling
ISO 10993-1: 2018	Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process
ISO 14971: 2019	Medical devices - Application of risk management to medical devices
IEC 62366-1: 2015 + AMD1:2020	Medical devices - Application of usability engineering to medical devices
ASTM D4169 - 16	Standard Practice for Performance Testing of Shipping Containers and Systems
ASTM F1980 - 16	Accelerated Aging testing

Use Steps	Use Steps Illustration	Use Steps Short Description
a	(b) (4)	**User removes the protective cap**
b		**User pushes the tip of the auto-injector against skin:** Pressing the auto-injector against the skin triggers an internal mechanism that automatically inserts the needle into the skin

Use Steps	Use Steps Illustration	Use Steps Short Description
c	(b) (4)	**Injection:** The needle penetrates the skin by pressing in the cover sleeve. As soon as the cover sleeve is completely pressed in, the drug delivery is triggered. This is signaled with an audible "click". The injection spring drives the syringe plunger such that the drug is injected. This process can be observed through the viewing window. As soon as the orange syringe plunger rod stops moving and is fully visible, the injection is complete. This is again signaled with an audible "click".
d		**User removes the Auto-injector from the skin:** As soon as the Auto-injector is removed from the skin, a spring pushes the cover sleeve back into a permanent locking position. This protects against accidental needlestick injuries. Once the Auto-injector is in locked mode, it can no longer be used.
e		**User disposes of the Auto-injector:** After use, the device is discarded in a sharps disposal container.

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The Sponsor has provided adequate device descriptions of the needle safety device and autoinjector.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

5. FILING REVIEW

CDRH performed Filing Review ☐ **Finalize Filing Review Section**	☐
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☑

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors	X		
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

Reviewer Comments: The Sponsor has provided adequate needle safety and autoinjector labeling and instructions for use.

6.2. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The Sponsor has provided adequate needle safety and autoinjector labeling and instructions for use.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		
Design Inputs/Outputs	**Yes**	**No**	**N/A**

Design requirements / specifications document present (essential performance requirements included)			
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X		
Bioequivalence Study utilized to-be-marketed device	X		
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

7.2. Design Inputs and Outputs

Essential Performance Requirements

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	N/A
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	N/A
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	Y
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y
ISO 11608-1: 2014 Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems	Y
ISO 11608-3: 2012 Needle-based injection systems for medical use - Requirements and test methods Part 3: Finished containers	Y
ISO 11608-5: 2012 Needle-based injection systems for medical use - Requirements and test methods Part 5: Automated Functions	Y
ISO 23908: 2011 Sharps Injury Protection – Requirements and test methods – Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	Y

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies:	**Mid-Cycle Deficiencies:**	**Final Deficiencies:**

☐ Yes ☑ No ☐ N/A	☐ Yes ☑ No ☐ N/A	☐ Yes ☑ No ☐ N/A
Reviewer Comments The Sponsor has followed all the applicable standards and testing for design control/performance testing.		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

8. RISK ANALYSIS

8.1. Risk Management Plan

Autoinjector for BLA761275 annex-r-2-3-13 Risk management report:

Reference Document Number Title
[1] FKSB-PL-MD-002 MSB11456 (Tocilizumab) Auto-injector - Risk Management Plan (RMP)
[2] FKSB-PL-MD-001 Design and Development Plan Tocilizumab auto-injector
[3] ISO 14971: 2019 Medical devices— Application of risk management to medical devices
[4] Global-SOP-ID-000003347 Risk Management Process for medical devices
[5] FKSB-SP-MD-110 Use Specification for MSB11456 Auto-injector
[6] 20460350 Document by (b) (4): Manufacturing, assembling and packaging process of Tocilizumab (b) (4) mg/mL pre-filled syringes with the (b) (4) safety device at (b) (4)
[7] 10094296 Document by (b) (4): Risk Management Plan
[8] 10094676 Document by (b) (4): Risk Management Report

Pre-filled Syringe with (b) (4)
references
[1] FKSB-PL-MD-019 MSB11456 (Tocilizumab) Pre-filled Syringe with (b) (4) Design & Development Plan
[2] 20289326 RISK MANAGEMENT REPORT – TOCILIZUMAB (MSB11456) PREFILLED SYRINGE WITH SAFETY SYSTEM
[3] FKSB-RAS-MD-007 MSB11456 (Tocilizumab) Pre-filled Syringe with (b) (4) Design Risk Assessment
[4] FKSB-RAS-MD-008 MSB11456 (Tocilizumab) Pre-filled Syringe with (b) (4) Process Risk Assessment
[5] 20289325 Risk Management Plan -Tocilizumab (MSB11456) Prefilled Syringe with Safety System
[6] Global-SOP-ID-
000003347 Risk Management Process for medical devices

Reviewer Comments
The Sponsor provided an adequate Risk Management Report for the PFS with safety device and autoinjector.

8.2. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The Sponsor provided an adequate and complete Risk Management Report for the PFS with safety device and autoinjector.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

Prefilled Syringe with Needle safety device testing summary.

EPR (source)	Acceptance criteria	Time zero	After Simulated Shipping	After Real Time Shipping	End of Shelf Life (accelerated aged devices)
Break loose Force (FNF 4.5.3)	F < (b) (4) N	Note (1) Pass* n=96 On 3 stability batches Mean = 5.8 N	Note (2) Not tested (tested after RT shipping)	Pass* n=30 Mean = 6.0 N Min. = (b) (4) N Max. = (b) (4) N	Note (3) Pass* Mean = 6.0 N
Cap Removal Force F_{RNS} (FNF 4.5.2)	(b) (4) N < F_{RNS} < (b) (4) N	Pass* n=100 Mean = 11.6 N Min. = (b) (4) N Max. = (b) (4) N	Note (2) Not tested (tested after RT shipping)	Pass* n=30 Mean = 9.1 N Min. = (b) (4) N Max. = (b) (4) N	Note (3) Pass* Mean = 18 N
Delivered Volume (FNF 4.5.3)	V ≥ (b) (4) mL	Pass* n = 60 Mean = 0.948 mL Min. = (b) (4) mL Max. = (b) (4) mL	Pass* n=60 Mean = 0.955 mL Min. = (b) (4) mL Max. = (b) (4) mL	Pass* n = 30 Mean = 0.947 mL Min. = (b) (4) mL Max. = (b) (4) mL	Pass* N = 72
Safety System Activation and Locking (FNF 4.5.5)	Activates at end of injection stroke and system is locked	Pass* n=100	Pass* n= 100	Pass* n= 149	Pass* N = 72
Extra activation Force (FNF 4.5.5)	F ≤ (b) (4) N	Pass* n=100 Mean = 2.7 N Min. = (b) (4) N Max. = (b) (4) N	Note (2) Not tested (tested after RT shipping)	Pass* N =30 Mean = 2.7 N Min. = (b) (4) N Max. = (b) (4) N	Pass* N = 72 Mean = 4.1 N Min. = (b) (4) N Max. = N
Override force (FNF 4.5.6)	F > (b) (4) N	Pass* n=30 Mean = 137 N Min. = (b) (4) N Max. = (b) (4) N	Note (2) Not tested (tested after RT shipping)	Pass* n= 149 Mean = 136 N Min. = (b) (4) N Max. = (b) (4) N	Pass* n= 72 Mean = 138 N Min. = (b) (4) N Max. = N

Autoinjector testing summary:

Table 7 Summary Report of EPRs and Results for MSB11456 AI

EPR	Acceptance criteria	Time Zero	After Simulated Shipping	After Real-Time Shipping	End of Shelf life (accelerated aged devices)
Cap Removal Force (FNF 11.28)	F_{CR} < (b) (4) N	Pass* n= 60 Mean = 13.6 N Minimum = (b) (4) N Maximum = (b) (4) N	Pass* n= 100 Mean = 12.9 N Minimum = (b) (4) N Maximum = N	Pass* n= 150 Mean = 12.9 N Minimum = (b) (4) N Maximum = N	Pass* n= 20 Mean = 13.0 N Minimum = (b) (4) N Maximum = N
Activation Force (FNF 11.30)	(b) (4) N < F_{Act} < (b) (4) N	Pass* n= 60 Mean = 6.6 N Minimum = (b) (4) N Maximum = N	Pass* n= 100 Mean = 8.3 N Minimum = (b) (4) N Maximum = N	Pass* n= 150 Mean = 8.2 N Minimum = (b) (4) N Maximum = N	Pass* n= 20 Mean = 6.6 N Minimum = (b) (4) N Maximum = N
Injection Time (FNF 11.24)	t_{Inj} < (b) (4) s	Pass* n= 60 Mean = 5.9 s Minimum = (b) (4) s Maximum = s	Pass* n= 100 Mean = 5.8 s Minimum = (b) (4) s Maximum = s	Pass* n= 150 Mean = 5.0 s Minimum = (b) (4) s Maximum = s	Pass* n= 20 Mean = 5.7 s Minimum = (b) (4) s Maximum = s
Delivered Volume (FNF 11.2)	Vol ≥ (b) (4) mL	Pass* n= 59 Mean = 0.94 mL Minimum = (b) (4) mL Maximum = mL	Pass* n= 100 Mean = 0.95 mL Minimum = (b) (4) mL Maximum = mL	Pass* n= 150 Mean = 0.95 mL Minimum = (b) (4) mL Maximum = mL	Pass* n= 60 Mean = 0.95 mL Minimum = (b) (4) mL Maximum = mL
Override Force (FNF 11.17)	F > (b) (4) N	Pass* n= 60 Note (1) All values > (b) (4) N	Pass* n= 100 Note (2) All values > (b) (4) N	Pass* n= 150 Note (2) All values > (b) (4) N	Pass* n= 50 Note (3) Mean = 259 N Minimum = (b) (4) N Maximum = N
Extended needle length (FNF 11-4)	(b) (4) mm	Pass* n= 60 Mean = 5.8 mm Minimum = (b) (4) mm Maximum = mm	Pass* n= 100 Mean = 5.7 mm Minimum = (b) (4) mm Maximum = mm	Pass* n= 150 Mean = 5.7 mm Minimum = (b) (4) mm Maximum = mm	Pass* n= 50 Mean = 6.1 mm Minimum = (b) (4) mm Maximum = mm
CCIT (FNF 13.7)	No dye entering the fluid path	Pass* n= 30	Pass* n= 40	Pass* n= 60	Note (4) Pass* n= 60

Updated 3-7-2023:

Essential Performance Requirement	Acceptance criteria
Cap Removal Force (F_{CR})	F_{CR} < (b) (4) N
Activation Force (F_{Act})	(b) (4) N < F_{Act} < (b) (4) N
Injection Time, t_{Inj}	t_{Inj} < (b) (4) s
Delivered Volume	V ≥ (b) (4) mL
Override Force	F > (b) (4) N
Extended needle length	(b) (4) mm
Container Closure Integrity	No dye ingress evidenced

Reviewer Comment

The Sponsor has completed adequate EPR testing with acceptable results that included aged devices and after shipping/transportation. Complete full reports are present under sections 3.2.R.1-1 through 3.19. medical device information and test reports.

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The Sponsor has completed adequate EPR testing with acceptable results that included aged devices and after shipping/transportation. Complete full reports are present under sections 3.2.R.1-1 through 3.19. medical device information and test reports. One IR was sent for Autoinjector Cap Removal force specification acceptance criteria was < (b)(4)N. We typically want this specification to be < (b)(4)N especially with Rheumatoid Arthritis patients. The Sponsor revised the specification to be < (b)(4)N.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent: 3/3/2023	**Date Received:** 3/7/2023
Information Request #1	The Autoinjector Cap Removal force specification acceptance criteria is < (b)(4)N. We typically want this specification to be < (b)(4)N especially with Rheumatoid Arthritis patients. Please revise your Autoinjector Cap Removal force specification acceptance criteria is < (b)(4)N.	
Sponsor Response	The company acknowledges FDA guidance and confirm implementation of the Cap Removal Force acceptance criteria to < (b)(4)N (Refer to Section 3.2.R.2.2 Administration Device – AI). New supporting documentation Section 3.2.R.2.2 Administration Device – AI, Replace	
Reviewer Comments	Sponsor's response is adequate. The Sponsor has updated their Autoinjector Cap Removal force specification documents to be a acceptance of < (b)(4)N.	
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Essential Performance Requirement	Acceptance criteria
Cap Removal Force (F_{CR})	F_{CR} < (b)(4)N
Activation Force (F_{Act})	(b)(4)N < F_{Act} < (b)(4)N
Injection Time, t_{Inj}	t_{Inj} < (b)(4)s
Delivered Volume	V ≥ (b)(4)mL
Override Force	F > (b)(4)N
Extended needle length	(b)(4)mm
Container Closure Integrity	No dye ingress evidenced

9.3. Discipline Specific Sub-Consulted Review Summary

☑ No Additional Discipline Specific Sub-Consults were requested
☐ The following additional Discipline Specific Sub-Consults were requested:

10. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☑

11.FACILITIES & QUALITY SYSTEMS

11.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☑
CDRH Facilities Inspection Review was not conducted	☐

11.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☑
CDRH Quality Systems Documentation Review was not conducted	☐

11.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts:

Prefilled Syringe with safety device and autoinjector.

The Sponsor provided the following production/manufacturing flow diagram that identifies the steps involved in the manufacture of the finished combination product. The diagram includes all steps involved in the manufacturing and assembly of the device constituent parts of the combination product:

Prefilled Syringe with safety device and autoinjector.

Reviewer Comments
Last inspection completed for Fresenius on 2/18/2020 with final decision of VAI. There were no ongoing or pending investigations or compliance actions. The Sponsor provided an adequate manufacturing process and production flow for the combination products under module 2 of the application.

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☒Yes	☐No

11.2.2. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission:

What Quality System did the Sponsor choose:

☐ Device QSR-based
☐ Drug cGMP-Based Streamline –
☑ Stream-line Both (no streamlined approach)

21 CFR 820.20 Summary of Management Responsibility	Firm(s): Fresenius Kabi	**Reviewer Discussion –Present in 1-27-23 IR response. Adequate**
21 CFR 820.30 Summary of Design Controls	Firm(s): Fresenius Kabi	**Reviewer Discussion – Present in 1-27-23 IR response.** Reviewed in detail in Section 7 The Design Control Process for Combination Products is described Fresenius Kabi's global procedure gSOP-PH-QM-004 Combination Products.

21 CFR 820.50 Summary of Purchasing Controls	Firm(s): Fresenius Kabi	**Reviewer Discussion – Present in 1-27-23 IR response.**
21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s): Fresenius Kabi	**Reviewer Discussion – Present in 1-27-23 IR response.** Reviewed in Section 12.2.3. The CAPA system is described in detail in Fresenius Kabi´s global procedure Event Handling & CAPA Process (Global-SOP-QM-000002473)
21 CFR 820.170 Summary of Installation	Firm(s): Fresenius Kabi	**Reviewer Discussion – N/A**
21 CFR 820.200 Summary Servicing	Firm(s): Fresenius Kabi	**Reviewer Discussion –N/A**
Subpart F – Identification and Traceability	Firm(s): Fresenius Kabi	**Reviewer Discussion – Present in 1-27-23 IR response.**
Subpart G – Production and Process Controls	Firm(s): Fresenius Kabi	**Reviewer Discussion – Present in 1-27-23 IR response.** Reviewed in Section 12.3
Subpart H – Acceptance Activities	Firm(s): Fresenius Kabi	**Reviewer Discussion – Present in 1-27-23 IR response.**
Subpart I – Nonconforming Product	Firm(s): Fresenius Kabi	**Reviewer Discussion – Present in 1-27-23 IR response.**
Subpart K – Labeling and Packaging Controls	Firm(s): Fresenius Kabi	**Reviewer Discussion – Present in 1-27-23 IR response.**
Subpart L – Handling, Storage, Distribution	Firm(s): Fresenius Kabi	**Reviewer Discussion – Present in 1-27-23 IR response.**
Subpart M – Records	Firm(s): Fresenius Kabi	**Reviewer Discussion – Present in 1-27-23 IR response.**
Subpart O – Statistical Techniques	Firm(s): Fresenius Kabi	**Reviewer Discussion – Present in 1-27-23 IR response.**

Reviewer Comments
The Sponsor provided complete and adequate GMP Quality Systems information in their 1-27-2023 IR response.

GMP Compliance Summary Conclusion		
The Sponsor provided adequate summary information about the GMP compliance activities	☑ Yes	☐ No

11.2.3. Corrective and Preventive Action Review

The Sponsor provided the following information with regards to corrective and preventive actions:

The CAPA system is described in detail in Fresenius Kabi´s global procedure Event Handling & CAPA Process (Global-SOP-QM-000002473)

The following table reflects whether the Sponsor addressed the required elements of corrective and preventive action controls:

CAPA Procedure Required Elements	Present
Procedures include requirements to analyze processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems.	Present in 2-24-2023 IR response.
Procedures include review and disposition process of nonconforming product, including documentation of disposition. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use.	Present in 2-24-2023 IR response.
Procedures include appropriate statistical analysis of these quality data to detect recurring quality problems	Present in 2-24-2023 IR response.
Investigations into the cause of nonconformities relating to product, processes, and the quality system	Present in 2-24-2023 IR response.
Includes requirements for identification and implementation of actions needed to correct and prevent recurrence of nonconformities and other quality problems	Present in 2-24-2023 IR response.
Verification or validation of the corrective and preventive actions taken to ensure that such action is effective and does not adversely affect the finished device	Present in 2-24-2023 IR response.
Each manufacturer shall establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications	Present in 2-24-2023 IR response.
Describes requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems	Present in 2-24-2023 IR response.
Ensures that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems	Present in 2-24-2023 IR response.
Submits relevant information on identified quality problems, as well as corrective and preventive actions, for management review	Present in 2-24-2023 IR response.
Requires documentation of all CAPA activities	Present in 2-24-2023 IR response.

Reviewer Comments: The Sponsor provided adequate CAPA procedure elements in their 2-24-2023 IR response.

BLA761275-Response to IR related to device
BLA761275-Response to IR related to device
BLA761275-Response to IR related to device
BLA761275-Response to IR related to device

CAPA Conclusion		
The Sponsor provided adequate information for corrective and preventive actions.	☒Yes	☐No

Essential Performance Requirements	Control Strategy Description - provide the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:
AI Cap removal force	(b) (4)

Essential Performance Requirements	Control Strategy Description - provide the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:
AI Activation Force	(b) (4)
AI Injection time	
AI Delivered volume	
	Final Release test (refer to Section 3.2.P.5.1 Specifications (PFS))
AI Override force	(b) (4)
AI Extended needle length	
(b) (4) Needle Safety System Activation and locking	
(b) (4) Extra activation force	(b) (4) however, this EPR was evaluated during verification (refer to Section 3.2.R.2.1 Administration Device – (b) (4)) and stability (refer to Section 3.2.P.8.1 Stability Summary and Conclusions (PFS) and Section 3.2.P.8.3.1 Stability Data (PFS)).
(b) (4) Override force	(b) (4) however, this EPR was evaluated during verification (refer to Section 3.2.R.2.1 Administration Device – (b) (4)) and stability (refer to Section 3.2.P.8.1 Stability Summary and Conclusions (PFS) and Section 3.2.P.8.3.1 Stability Data (PFS)).

11.3. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☑ No ☐ N/A	Final Deficiencies: ☐ Yes ☑ No ☐ N/A
Reviewer Comments		

Sponsor did not provide quality systems information. IR sent 1-24-2023.
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No

	Date Sent: 1/24/2023	**Date/Sequence Received:** 1/27/2023
Information Request #1	I am unable to locate elements of your GMP compliance approach included in submission and which Quality Systems were performed for the final finished combination products, PFS with needle safety device and autoinjector such as: 21 CFR 820.20 Summary of Management Responsibility 21 CFR 820.30 Summary of Design Controls 21 CFR 820.50 Summary of Purchasing Controls 21 CFR 820.100 Summary of Corrective and Preventive Actions 21 CFR 820.170 Summary of Installation 21 CFR 820.200 Summary Servicing Subpart F – Identification and Traceability Subpart G – Production and Process Controls Subpart H – Acceptance Activities Subpart I – Nonconforming Product Subpart K – Labeling and Packaging Controls Subpart L – Handling, Storage, Distribution Subpart M – Records Subpart O – Statistical Techniques	
Sponsor Response	The Sponsor provided responses to all of the above. EDR Location: \\CDSESUB1\evsprod\BLA761275\0021	
Reviewer Comments	Sponsor's response is adequate.	
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

	Date Sent: 2/21/2023	**Date Received:** 2/24/2023
Information Request #2	We are unable to locate the CAPA procedure required elements for the device constituent parts/combination products. Please provide the following CAPA Procedure Required Elements.	
Sponsor Response	BLA761275-Response to IR related to device BLA761275-Response to IR related to device BLA761275-Response to IR related to device BLA761275-Response to IR related to device	
Reviewer Comments	Sponsor's response is adequate. Sponsor provided the required CAPA procedure required elements.	
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

	Date Sent: 3/3/2023	**Date Received:** 3/7/2023

Information Request #3	We were unable to locate control strategy for the device constituent EPRs. Please provide the control strategy information regarding the EPRs of the device constituents in a table form like the example provided.
Sponsor Response	

Essential Performance Requirements	**Control Strategy Description - provide the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:**
AI Cap removal force	(b) (4)

Essential Performance Requirements	**Control Strategy Description - provide the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:**
AI Activation Force	(b) (4)
AI Injection time	
AI Delivered volume	Final Release test (refer to Section 3.2.P.5.1 Specifications (PFS))
AI Override force	(b) (4)
AI Extended needle length	
(b) (4) Needle Safety System Activation and locking	
(b) (4) Extra activation force	(b) (4) however, this EPR was evaluated during verification (refer to Section 3.2.R.2.1 Administration Device – (b) (4)) and stability (refer to Section 3.2.P.8.1 Stability Summary and Conclusions (PFS) and Section 3.2.P.8.3.1 Stability Data (PFS)).
(b) (4) Override force	(b) (4) however, this EPR was evaluated during verification (refer to Section 3.2.R.2.1 Administration Device – (b) (4)) and stability (refer to Section 3.2.P.8.1 Stability Summary and Conclusions (PFS) and Section 3.2.P.8.3.1 Stability Data (PFS)).

Reviewer Comments	Sponsor's response is adequate.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

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/s/

SUSIE B CHOI
05/30/2023 11:53:31 AM

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

PATIENT LABELING REVIEW

Date:	May 24, 2023
To:	Susie Choi, PharmD Regulatory Health 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)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (nonproprietary name):	[MSB11456] TYENNE (tocilizumab-aazg)[1]
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761275
Applicant:	Fresenius Kabi USA, LLC

1 INTRODUCTION

[1] MSB11456 has been developed as a proposed biosimilar to US-licensed Actemra (tocilizumab). The proposed proprietary name Tyenne was found conditionally acceptable on November 30, 2022. The nonproprietary name "tocilizumab-aazg" was found conditionally acceptable on March 2, 2023.

On May 30, 2022, Fresenius Kabi USA, LLC submitted for the Agency's review an original Biologics License Application (BLA) 761275 for [MSB11456] TYENNE (tocilizumab-aazg) injection, for subcutaneous use. The Applicant seeks approval for [MSB11456] TYENNE (tocilizumab-aazg) as a biosimilar product to US-licensed ACTEMRA (tocilizumab) injection, for intravenous or subcutaneous use, licensed under BLA 125472 by Genentech, Inc.

The Applicant proposes TYENNE (tocilizumab-aazg) injection, for subcutaneous use to be licensed for the same indications as the single reference product ACTEMRA (with the exception of those indications under orphan drug exclusivity), for the treatment of the following:

- **Rheumatoid Arthritis (RA):** Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
- **Giant Cell Arteritis (GCA):** Adult patients with giant cell arteritis.
- **Polyarticular Juvenile Idiopathic Arthritis (PJIA):** Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.
- **Systemic Juvenile Idiopathic Arthritis (SJIA):** Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

On August 4, 2022, the Division of Rheumatology and Transplant Medicine (DRTM) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for TYENNE (tocilizumab-aazg) injection, for subcutaneous use.

This memorandum documents the DMPP review deferral of the Applicant's proposed MG and IFUs for TYENNE (tocilizumab-aazg) injection, for subcutaneous use.

2 CONCLUSIONS

DMPP completed a review of TYENNE (tocilizumab-aazg) injection MG and IFUs for BLA 761275 and sent our review documents to DRTM on May 18, 2023, for clearance. However, due to outstanding facility inspection deficiencies, DRTM plans to issue a Complete Response (CR) letter. A final review of the MG and IFUs will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

MARY E CARROLL
05/24/2023 02:19:41 PM

MARCIA B WILLIAMS
05/24/2023 02:22:25 PM

LASHAWN M GRIFFITHS
05/24/2023 02:27:52 PM

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

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

Memorandum

Date: May 16, 2023

To: Susie Choi, Senior Regulatory Project Manager
Division of Rheumatology and Transplant Medicine

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

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for TYENNE® (tocilizumab-aazg) injection, for subcutaneous use

BLA: 761275

Background:
In response to DRTM's consult request dated August 3, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original BLA submission for TYENNE® (tocilizumab-aazg) injection, for subcutaneous use.

PI/Medication Guide/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on May 8, 2023, and our comments are provided below.

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 accessed from SharePoint on May 8, 2023, 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.

53 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

KYLE SNYDER
05/16/2023 10:41:57 AM

MEMORANDUM

HUMAN FACTORS STUDY RESULTS REVIEW MEMO

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 17, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761275
Product Name, Dosage Form, and Strength:	Tyenne (tocilizumab-aazg)[a] Injection, 162 mg/0.9 mL
Applicant/Sponsor Name:	Fresenius Kabi
TTT ID #:	2022-2099-1
DMEPA 1 Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES

1 PURPOSE OF MEMORANDUM

On April 14, 2023, the Applicant submitted a revised instructions for use (IFU) for Tyenne. Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised IFU for Tyenne (see Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous human factors validation results review.[b]

2 CONCLUSION

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

[a] Tyenne has been developed as a proposed biosimilar to US-licensed Actemra (tocilizumab). The proposed proprietary name, Tyenne was found conditionally acceptable on November 30, 2022, and the nonproprietary name for this BLA, tocilizumab-aazg, was found conditionally acceptable on March 3, 2023.

[b] Bhalodia, A. Human Factors Study Results Review for Tyenne (BLA 761275). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAR 30. TTT ID No.: 2022-2099.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 14, 2023

Instructions for use (Image not shown) available from:
\\CDSESUB1\EVSPROD\bla761275\0039\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-ai.pdf

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/s/

AVANI BHALODIA
04/17/2023 08:32:50 AM

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04/17/2023 08:40:38 AM

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 13, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761275
Product Name, Dosage Form, and Strength:	Tyenne (tocilizumab- aazg)[a] Injection, 80 mg/4 mL(20 mg/mL), 200 mg/10 mL (20mg/mL), 400 mg/20 mL(20 mg/mL), 162 mg/0.9 mL
Applicant/Sponsor Name:	Fresenius Kabi
TTT ID #:	2022-2098-4
DMEPA 1 Safety Evaluator:	Teresa McMillan, PharmD
DMEPA 1 Team Leader:	Idalia Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on April 6, 2023 for Tyenne. Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container label and carton labeling for Tyenne (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

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

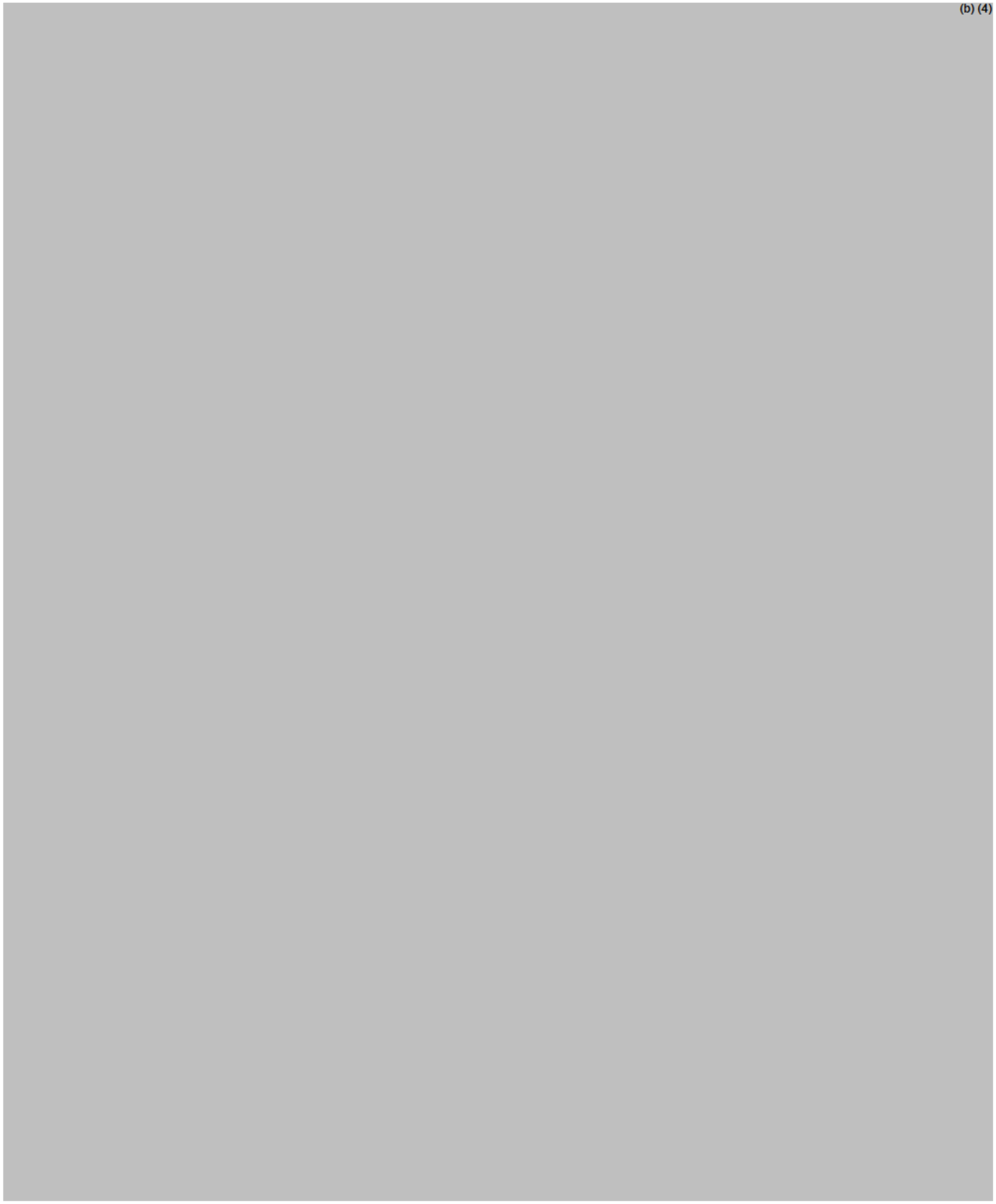
[a] The proposed proprietary name, Tyenne was found conditionally acceptable on November 30, 2022. The nonproprietary name, tocilizumab- aazg was found conditionally acceptable on March 3, 2023.

[b] McMillan, T. Label and Labeling Review for Tyenne (BLA 761275). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAR 30. TTT ID No.: 2022-2098-3.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 6, 2023

Container labels

(b) (4)



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/s/

TERESA S MCMILLAN
04/13/2023 09:55:04 AM

IDALIA E RYCHLIK
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HUMAN FACTORS STUDY REPORT 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 30, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761275
Product Type:	Combination Product
Product Name, Dosage Form, and Strength:	Tyenne (tocilizumab-aazg)[1] Injection 162 mg/0.9 mL
Device Constituent:	Autoinjector
Rx or OTC:	Rx
Applicant/Sponsor Name:	Fresenius Kabi
Submission Date:	May 31, 2022; January 27, 2023; February 7, 2023
TTT ID #:	2022-2099
DMEPA 1 Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

[1] Tyenne has been developed as a proposed biosimilar to US-licensed Actemra (tocilizumab). The proposed proprietary name, Tyenne was found conditionally acceptable on November 30, 2022 and the nonproprietary name for this BLA, tocilizumab-aazg, was found conditionally acceptable on March 3, 2023.

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study results report submitted under BLA 761275 for Tyenne (tocilizumab-aazg) injection.

1.1 PRODUCT DESCRIPTION

Table 1. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	interleukin-6 (IL-6) receptor antagonist
Nonproprietary Name	tocilizumab-aazg
Indication	Rheumatoid Arthritis (RA) • Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs). Giant Cell Arteritis (GCA) • Adult patients with giant cell arteritis. Polyarticular Juvenile Idiopathic Arthritis (PJIA) • Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis (SJIA) • Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.
Route of Administration	for intravenous or subcutaneous use
Dosage Form	Subcutaneous injection and intravenous infusion
Strength	Subcutaneous Injection Injection: 162 mg/0.9 mL in a single-dose prefilled syringe or single-dose prefilled autoinjector Intravenous Infusion Injection: 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to intravenous infusion
Dose and Frequency	For RA, PJIA and SJIA, Tyenne may be used alone or in combination with methotrexate: and in RA, other DMARDs may be used. Rheumatoid Arthritis Recommended Adult Intravenous Dosage: When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg per

kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.

Recommended Adult Subcutaneous Dosage:

Patients less than 100 kg weight	162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response
Patients at or above 100 kg weight	162 mg administered subcutaneously every week

Giant Cell Arteritis

Recommended Adult Intravenous Dosage:

The recommended dose is 6 mg per kg every 4 weeks in combination with a tapering course of glucocorticoids. Tyenne can be used alone following discontinuation of glucocorticoids.

Recommended Adult Subcutaneous Dosage:

The recommended dose is 162 mg given once every week as a subcutaneous injection, in combination with a tapering course of glucocorticoids.

A dose of 162 mg given once every other week as a subcutaneous injection, in combination with a tapering course of glucocorticoids, may be prescribed based on clinical considerations.

Tyenne can be used alone following discontinuation of glucocorticoids.

Polyarticular Juvenile Idiopathic Arthritis:

Recommended Intravenous PJIA Dosage Every 4 Weeks	
Patients less than 30 kg weight	10 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Recommended Subcutaneous PJIA Dosage	
Patients less than 30 kg weight	162 mg once every three weeks
Patients at or above 30 kg weight	162 mg once every two weeks

Systemic Juvenile Idiopathic Arthritis:

<table>
<tr><td></td><td>
<table>
<tr><th colspan="2">Recommended Intravenous SJIA Dosage Every 2 Weeks</th></tr>
<tr><td>Patients less than 30 kg weight</td><td>12 mg per kg</td></tr>
<tr><td>Patients at or above 30 kg weight</td><td>8 mg per kg</td></tr>
</table>

<table>
<tr><th colspan="2">Recommended Subcutaneous SJIA Dosage</th></tr>
<tr><td>Patients less than 30 kg weight</td><td>162 mg every two weeks</td></tr>
<tr><td>Patients at or above 30 kg weight</td><td>162 mg every week</td></tr>
</table>
</td></tr>
<tr><td>How Supplied</td><td>For Intravenous Infusion
<u>Single-Dose Vial</u>
Each carton contains one vial. Each vial is supplied as 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL solution for further dilution prior to intravenous infusion. The vial stopper is (b) (4).

For Subcutaneous Injection
<u>Prefilled Syringe</u>
Each carton contains (b) (4) a single-dose prefilled syringe delivering 162 mg/0.9 mL of Tyenne. The syringe plunger stopper and needle cover are not made with natural rubber latex.
<u>Autoinjector</u>
Each carton contains (b) (4) a single-dose autoinjector delivering 162 mg/0.9 mL of Tyenne. The syringe plunger stopper and needle cover are (b) (4).</td></tr>
<tr><td>Storage</td><td>Must be refrigerated at 36°F to 46°F (2°C to 8°C). Do not freeze. A single prefilled syringe or autoinjector may be stored at (b) (4) 77°F (25°C) for a single period of up to 14 days. (b) (4) Protect the vials, syringes, and autoinjectors from light by storage in the original package until time of use and keep syringes and autoinjectors dry.</td></tr>
<tr><td>Container Closure/Device Constituent</td><td>Single-Dose Vial
Prefilled Syringe</td></tr>
</table>

	Autoinjector (b) (4)
Intended Users	Patients; caregivers; HCPs
Intended Use Environment	Home; clinical setting

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

- On June 12, 2020, the Applicant submitted their HF validation study protocol under IND 129965 for MSB 11456 (a proposed biosimilar to US-licensed Actemra) injection 162 mg/0.9 mL autoinjector (AI). We reviewed the protocol and provided recommendations.[2]
- On October 29, 2020 and December 7, 2020 respectively, the Applicant submitted two clarifying questions in response to recommendations that we made during a previous HF protocol review.[2] We reviewed the questions and provided responses.[3]
- On May 31, 2022, the Applicant submitted a biologics license application (BLA) for Tyenne (tocilizumab-aazg) injection under BLA 761275. This submission included HF validation study results reports, which is the subject of this review.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

Table 2. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	Section 1.1
Background Information Previous DMEPA HF Reviews	A
Background Information on Human Factors Engineering (HFE) Process	B
Human Factors Validation Study Report	C

[2] Barlow M. HF Protocol Review for MSB 11456 (IND 129965). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 21. RCM No.: 2020-1243.

[3] Barlow M. HF Protocol Clarifying Questions Review for MSB 11456 (IND 129965). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 17. RCM No.: 2020-1243-1.

Table 2. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Information Requests Issued During the Review	D
Labels and Labeling	E

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our analysis to determine if the results indicate that the user interface supports the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

Table 3 presents a summary of the HF validation study design. See Appendix B and C for more details on the study design.

Table 3. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details
Participants	• 15 adult patients diagnosed with rheumatoid arthritis (RA) • 15 adult patients diagnosed with giant cell arteritis (GCA) or surrogate conditions • 15 adolescent patients with juvenile idiopathic arthritis (JIA) • 15 lay injection naïve caregivers • 15 lay injection experienced caregivers • 15 healthcare professionals (HCPs)
Training	Study participants did not receive training on how to use the device during the study.
Test Environment	The study environment simulated a home environment or a doctor's office. To the extent that the test facilities permitted, the rooms were illuminated by overhead incandescent and/or fluorescent lights producing a lighting level in the range of approximately 200 to 500 Lux, comparable to a well-lit room at home or a room in a doctor's office. The test rooms were relatively quiet, comparable to a library reading room. However, there were occasional unplanned acoustic distractions, such as telephones ringing, doors opening and closing, footsteps, and cars driving by the facility. These noises were infrequent and quite muted. The average continuous sound level at desktop level was about 30 to 35 dBA with maximum impulse sound exposures of up to 45 dBA (the sound pressure level in a quiet room).

	The study rooms had one-way mirrors on one wall, enabling observers (e.g., data collectors and observers) on the other side of the mirror to observe and listen to the study sessions. To simulate distractions that users might encounter during real-world tocilizumab autoinjector use, the moderator introduced one distraction when the participant was performing the injection administration during the first use scenario. Specifically, the moderator initiated a short telephone ring and apologized for the disturbance.
Sequence of Study	Scenario 1: simulated use of first injection (IFU optional) Root cause discussion Knowledge assessment Root cause discussion Scenario 2: simulated use of second injection (IFU mandatory) Root cause discussion

2.2 DISCUSSION

2.2.1 USER GROUPS

During the course of our review, we noted that the Applicant did not recruit the recommended stratification of injection experienced (seven) and injection naïve participants (eight) within the adult RA patient user group. We noted that four injection naïve and eleven injection experienced participants were recruited within the adult RA patients user group. However, the Applicant did not provide their rationale for not recruiting the recommended number of injection naïve (eight) participants for the adult RA patient user group. Thus, on February 2, 2023, we issued an information request (IR) to request their rationale for not recruiting the recommended number of injection naïve and injection experienced participants within the adult RA patient user group.

In the Applicant's IR response dated February 7, 2023, they indicated that the recruiting efforts spanned 23 cities in the US and several participants were not interested in participating due to the COVID pandemic and related risks of contamination. Additionally, the Applicant indicated that there were three injection naïve RA patients who were scheduled to participate and dropped out of the study with no notice the day of their session. Furthermore, the Applicant had a strict inclusion criteria for the injection naïve user group. Specifically, the recruitment staff were required to find RA patients who do not inject as part of their treatment and who have never participated in a study related to injectable devices. Also, the Applicant indicated that the criterion for hand dexterity impairment terminated anyone that was near remission. We note we did not make the aforementioned hand dexterity impairment criterion recommendation. Regarding the impact of not recruiting more injection naïve participants on the study, the Applicant stated,

"*Based on the results of the human factors validation study, the injection experienced RA participants exhibited a higher error rate than the injection naïve RA participants.*

The experienced participants committed 29 use errors, while the naïve participants committed 7 use errors. Adjusted for the different group sizes, 11 experienced versus 4 naïve participants, it shows that 60% of the use errors were committed by the experienced participants, while only 40% of the use errors were committed by the naïve participants.

Of the 7 use events experienced by injection naïve RA participants, 4 were shared with other participants. The remaining 3 were due to IFU Design, and Ambiguous Device Feedback. All 3 were not specifically tied to them being injection naïve.

The presented device design ((b) (4)) is used in auto-injectors (AIs) on the market. For example, (b) (4) is also used for Rheumatoid Arthritis. Given that this is a proven design, it is safe to estimate that naïve users can use it safely and efficiently, while the higher potential for use errors is expected in injection experienced users due to negative transfer from previously used devices.

Therefore, the use of 4 injection experienced RA participants instead of 4 injection naïve participants did increase the number of observed use events, thus presenting a more conservative study approach, i.e., a worse-case approach, than having the initial target of 8 injection naïve RA participants.

In addition, the study included 2 injection naïve Giant Cell Arteritis (GCA) patients. While GCA patients exhibit related symptoms to RA patients, a subset of symptoms is shared by both populations, i.e., fatigue, fever, polymyalgia rheumatica. Therefore, it is reasonable to assume that use errors exhibited by the injection naïve GCA participants will be comparable to use errors exhibited by the injection naïve RA participants."

In conclusion, the Applicant indicated that despite the extensive recruiting effort, reaching the recruiting target of 50% injection naïve and injection experienced participants proved to be infeasible and therefore, four injection experienced participants were recruited instead of four injection naïve participants to reach the overall recruiting target of 15 RA participants. Additionally, the Applicant concluded that having four additional injection experienced RA participants instead of four injection naïve RA participants did not negatively affect the validity of the study results. Based on the Applicant's response above, in this particular instance, based on the COVID-19 pandemic circumstance and difficulty in recruiting injection naïve RA participants, we find the inclusion of four additional injection experienced RA participants instead of four injection naïve RA participants to reach the overall recruiting target of 15 RA participants reasonable.

Additionally, the Applicant indicated that one GCA patient who did not meet some of the intended injection criteria was included due to difficulty recruiting GCA patients because these patients are difficult to recruit. This participant had previous experience administering

injections to animals (on an annual basis) and was categorized as injection experienced. The Applicant indicated that this protocol deviation did not negatively impact the ability of the study to meet its goals because this patient had been diagnosed with GCA and met all other necessary screening criteria, thus qualifying her as an intended user of the product and reducing the need to test surrogates. Additionally, the Applicant indicated that this non-traditional injection experience was representative of the variety of injection experiences a given patient population may have prior to self-administering a product.

We are unable to align with the Applicant's categorization of the abovementioned participant as injection experienced because we do not consider a user who administers injections on an annual basis to be an injection experienced user. However, given the rarity of these GCA patients and the fact that the participant met all other necessary screening criteria, in this particular instance, we find it reasonable to include the abovementioned participant.

3 RESULTS AND ANALYSES

We have carefully reviewed each observed event, the Applicant's URRA, the participants' subjective feedback, the Applicant's RCA, the Applicant's comments and proposed mitigations below.

Table 4. Focused Analysis of Use Errors, Use Difficulties and Close Calls and DMEPA's Recommendations

Legend: **UE** = use error; **CC** = close call; **UD** = use difficulty; **URRA** = use-related risk analysis; **RCA** = root cause analysis
Scenario Type: Scenario 1: Simulated-use of first injection (IFU optional), Knowledge assessment, Scenario 2: Simulated-use of second injection (IFU mandatory)
Participants ID: RE = injection experienced adult patients with rheumatoid arthritis (RA), RN = injection naive adult patients with RA, GE = injection experienced adult patients with giant cell arteritis (GCA), GN = injection naïve adult patients with GCA, JE = injection experienced adolescent patients with juvenile idiopathic arthritis (JIA), JN = injection naïve adolescent patients with JIA, CE = injection experienced adult lay caregivers, CN = injection naïve adult lay caregivers, HC = injection experienced healthcare professionals

Information Supplied by Applicant	DMEPA's Findings and Recommendations
Task: Hold the device against the skin at the injection site Errors: / Participant Type: / Scenario UE (n=17) / CE = 3, CN = 2, GN = 2, HC = 1, JN = 2, RE = 1, RN = 2 / 1 UD (n=2) / CN = 1, JE = 1 / 1 UE (n=2) / CE = 1, RN = 1 / 2 Observed error(s): UE: some participants did not correctly hold the device against the skin at the injection site until the second click. Some participants did not complete this step because of an error in a previous task. UD: participants turned the device during the injection. Risk associated with Task Errors (Per Applicant URRA): if this task is omitted or performed incorrectly, it may lead to underdose which may lead to: • reduced therapeutic efficacy • disease progression Relevant RCA/Subjective Feedback/Observation: • Negative transfer: participants based injection length on previous experience administering other medications. • Test artifact: participant did not understand that the test devices were functional. Another participant was unsure if device was injecting because he could not feel the needle in his skin. • Ambiguous device feedback: participants thought the first click indicated the completion of the injection.	
Applicant Comment and Proposed Mitigations: The Applicant added the phrase "keep holding down" in between images in Figures N, O and P respectively (see image below), to instruct the user to keep holding down the AI until the injection is complete.	We acknowledge the Applicant's proposed mitigation strategy and find it reasonable; however, our review of the instructions for use (IFU) indicates that, Step 6.6 instructions as presented (i.e., text and figure) does not define the meaning of "first click". Based on the subjective feedback (participants thought the first click indicated the completion of the injection), and our overall assessment, we find that the IFU Step 6.6 can be improved to better

<table>
<tr><td></td><td>convey the meaning of the “first click”. We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing data for Agency review.</td></tr>
<tr><td>KBA question: “What can you do to help remember where to inject on your next injection? [Record your injection]”
<table><tr><td>Errors:</td><td>Participant Type:</td></tr><tr><td>Incorrect (n=21)</td><td>CE = 5, CN = 6, GN = 1, HC = 2, JE = 2, JN = 2, RE = 1, RN = 2</td></tr></table>Observed error(s):
Incorrect: participants didn’t verbally acknowledge that the injection site must be recorded so as to remember where they injected.
Risk associated with Task Errors (Per Applicant URRA): if this task is omitted or performed incorrectly, it may lead to the user using the same injection site which may lead to injection site reaction, mild redness, local erythematous eruption that may become pruritic, itchy, and sometimes painful, blistering.
Relevant RCA/Subjective Feedback/Observation:
IFU layout: participants did not recognize that the IFU had not been fully unfolded due to the IFU layout.
Information location: participants expected this information to be recorded when selecting an injection site in Step 4.
Information volume: although the participant read the step, he forgot the instruction due to the amount of information in the IFU.</td><td></td></tr>
</table>

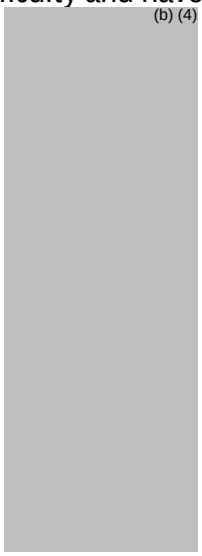
• Negative transfer: participants used their previous experience administering other medications. • Incorrect mental model: participants thought that it was not necessary to fully read the IFU, either because they assumed someone else would be responsible for the preparation and disposal steps or because they had previous experience administering injections. • Insufficient salience of IFU step: participants did not state to record the injection because they did not notice the instruction or did not notice all content stated in the instruction. • Insufficient illustration: participant believed the illustration in Step 9 meant to write down how the injection went or to write a letter to their doctor rather than to record the date and location. • Test artifact: typical materials not available in study environment or participant assumed next steps were not as important due to simulated use scenario.	
Applicant Comment and Proposed Mitigations: The Applicant added a small arrow to the bottom of each panel in the IFU indicating to continue to the next section in order to more clearly indicate when the instructions have been fully unfolded.	We acknowledge the Applicant's proposed mitigation strategy and find it reasonable; however, our review of the IFU indicates that, the image in Step 9, Figure V does not explicitly instruct users to record the injection date and site. Based on the subjective feedback (participants thought the image in Step 9, Figure V meant to write down how the injection went or to write a letter to their doctor), and our overall assessment, we find that the image in IFU Step 9, Figure V can be improved to better depict recording the injection date and site. We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing data for Agency review.

3.1 ANALYSIS OF OTHER CRITICAL AND NON-CRITICAL TASK ERRORS

The HF validation study showed use errors, use difficulties, and close calls with the tasks listed below in this section; however, based on our review of the available assessment of these use errors/use difficulties/close calls, the available participants' subjective feedback, the Applicant's root cause analysis and the Applicant's mitigation strategies, we determined the residual risk is acceptable. Specifically, users did not provide subjective feedback that indicated any potential issues with the user interface for the tasks identified. Based on our assessment, we find that the labeling mitigations in place include information that is prominently placed within the labels and labeling to address the tasks below. Subsequently, we did not identify further need for risk mitigation strategies at this time to address the use errors related to the following tasks and find the residual risks are acceptable:

- Prepare a clean surface
- Check expiration date on carton
- Open the box and remove the IFU and the sealed blister from the box, check blister for damage, and check expiration date on the blister
- Peel the sealed blister and invert the blister to remove the AI from the blister
- Use the auto-injector within 8 hours after removing it from the refrigerator
- Check device condition
- Check the medication name and expiration date
- Check drug condition
- Wash hands
- Select an appropriate injection site
- Clean selected injection site
- Remove cap
- Throw away the clear cap
- Position the device at 90 degrees to the injection site: there were seven use errors (note: one participant had an error in a previous task that prevented her from completing this task), one close call and two use difficulties observed for this task. The root cause analysis indicated that these use errors, close call and use difficulties were due to negative transfer (from other pre-filled pens), first time use (unsure of the method to activate the injection) and incorrect mental model (participant thought he had to tilt the device to improve medication flow). Based on our review of the user interface, we did not identify any additional mitigations to address these use errors, close call and use difficulties and have no recommendations at this time.
- Push device against the skin to activate injection (hear 1st click): There were four use errors (note: all four participants had errors in a previous task that prevented them from completing this task) and two use difficulties observed for this task. The root cause analysis indicated that these use difficulties were due to negative transfer (from current device use) and first-time use (participant did not know how firmly to press down on the device because she was performing an injection for the very first time). Based on our review of the user interface, we did not identify any additional mitigations to address these use errors and use difficulties and have no recommendations at this time.

- Wait 5 seconds after injection is complete (count to 5): There were 29 use errors (note: 17 out of the 29 use errors were attributed to participants not completing this task because of an error in a previous task) and one use difficulty observed for this task. The root cause analysis indicated that these use errors and use difficulty were due to negative transfer (from current device use), insufficient illustration (individual illustrations M, N, and O led to confusion about overall time required for injection), ambiguous device feedback (second click indicated to participant that medication had been injected), incorrect mental model (participants thought they held for 5 seconds but they did not) and slip (participant understood instruction but forgot to perform step). The Applicant added the phrase "*keep holding down*" in between images in Figures N, O and P respectively, (see image below) to instruct the user to keep holding down the AI until the injection is complete. Based on our review of the user interface, we did not identify any additional mitigations to address these use errors and use difficulty and have no recommendations at this time.



- Check that the full injection dose has been delivered: There were 11 use errors (note: all use errors were attributed to participants not completing this task because of an error in a previous task) and one use difficulty observed for this task. The root cause analysis indicated that this use difficulty was due to exerting additional caution (the participant was confused because she previously did not hear the second click, she was unsure if she could remove the AI from the injection site, leading her to hold the AI in place longer than necessary). Based on our review of the user interface, we did not identify any additional mitigations to address these use errors and use difficulty and have no recommendations at this time.
- Lift device from injection site
- Treat the injection site after the injection
- Discard used device into a sharps container
- Do not use the AI if it has been dropped
- If you do not receive a full dose of medication, call your healthcare provider. Do not perform a second injection.
- Keep the AI out of reach and sight of children

3.2 LABELS AND LABELING

Table A below include the identified medication error issues with the submitted instructions for use (IFU) based on the HF study results, our rationale for concern, and the proposed recommendation to minimize the risk for medication error. Additionally, we note that the DMEPA 1 primary review team evaluated product specific label and labeling under separate cover and label and labeling comments have been sent to the Applicant based on the outcome of that review.[4]

[4] McMillan, T. Label and Labeling Review for Tyenne (BLA 761275). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 DEC 15. RCM No.: 2022-2098.

Table A: Identified Issues and Recommendations for Fresenius Kabi (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU)			
1.	Step 6.6 does not include information regarding the meaning of the first click.	Per the URRA, if the user does not hold the device against the injection site, there is a risk of underdose which may lead to reduced therapeutic efficacy and disease progression. The human factors (HF) validation study results identified subjective feedback that indicated that some participants thought the first click indicated the completion of the injection.	We recommend including the meaning of the first click in Step 6.6.
2.	Step 9, Figure V does not explicitly instruct users to record the injection date and site. (b) (4)	Per the URRA, if the user does not record their injection to help remember where to inject on their next injection, there is a risk of using the same injection site which may lead to injection site reaction, mild redness, local erythematous eruption that may become pruritic, itchy, and sometimes painful, blistering.	Revise the image in Figure V to include the language “Date of Administration:” and “Injection Site:”. Additionally, consider including example date(s) and site(s) for users to reference.

		The HF validation study results identified subjective feedback that indicated that participants thought the image in Step 9, Figure V meant to write down how the injection went or to write a letter to their doctor.	

4 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated several use errors, close calls, use difficulties with critical tasks that may result in harm. Based on our review of the available participants' subjective feedback, and root cause analysis, we identified additional risk mitigations to address the use errors. 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 validation testing data for Agency review.

4.1 RECOMMENDATIONS FOR FRESENIUS KABI

Our evaluation of your human factors (HF) validation study 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 label and labeling for our review. We have determined that in this instance, you may implement these revisions without submitting additional human factors validation data for Agency review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. BACKGROUND INFORMATION

A.1 PREVIOUS HF REVIEWS

A.1.1 Methods

On July 13, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, "IND 129965", "BLA 761275" and "MSB 11456".

A.1.2 Results

Our search identified two previous reviews[2,3], and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX B. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in EDR via:
\\CDSESUB1\evsprod\bla761275\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\rheumatoidarthritis\5354-other-stud-rep\msb11456\auto-injector\human-factors-usability-engineering-hf-ue-report-msb11456-to.pdf

APPENDIX C. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:
\\CDSESUB1\evsprod\bla761275\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\rheumatoidarthritis\5354-other-stud-rep\msb11456\auto-injector\human-factors-summative-validation-study.pdf

APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On January 24, 2023, we issued an information request (IR) to clarify the inconsistency between the information on how long the autoinjector should not be kept out of the refrigerator without use in the HF usability engineering report and the IFU. We recommended the Applicant revise their IFU accordingly to correctly include information on how long the autoinjector should not be kept out of the refrigerator without use.
The Applicant provided an acceptable response on January 27, 2023, that can be accessible in EDR via: \\CDSESUB1\EVSPROD\bla761275\0020\m1\us\111-info-amend\responses-to-questions-ir15-hf-and-ifu-received-jan-24-2023.pdf

On February 2, 2023, we issued an IR to request the Applicant's rationale for not recruiting the recommended number of injection naïve and injection experienced participants for the adult RA patient user group.
The Applicant provided a response on February 7, 2023, that can be accessible in EDR via:
\\CDSESUB1\EVSPROD\bla761275\0024\m1\us\111-info-amend\responses-to-questions-ir-17-device-hfs.pdf

APPENDIX E. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[5] along with postmarket medication error data, we reviewed the following Tyenne labels and labeling submitted by Fresenius Kabi on May 31, 2022.

- Carton labeling
- Container label(s)
- Instructions for Use (Image not shown). Available from: \\CDSESUB1\evsprod\bla761275\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-ai.pdf

E.2 Label and Labeling Images

Carton Labeling

(b) (4)

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

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JASON A FLINT
04/03/2023 11:44:00 AM

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 30, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761275
Product Name, Dosage Form, and Strength:	Tyenne (tocilizumab- aazg)[a] Injection, 80 mg/4 mL(20 mg/mL), 200 mg/10 mL (20mg/mL), 400 mg/20 mL(20 mg/mL), 162 mg/0.9 mL
Applicant/Sponsor Name:	Fresenius Kabi
TTT ID #:	2022-2098-3
DMEPA 1 Safety Evaluator:	Teresa McMillan, PharmD
DMEPA 1 Team Leader:	Idalia Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 21, 2023 for Tyenne. Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container label and carton labeling for Tyenne (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. We provide recommendations in Section 3 Recommendations for Fresenius Kabi.

[a] The proposed proprietary name, Tyenne was found conditionally acceptable on November 30, 2022. The nonproprietary name, tocilizumab- aazg was found conditionally acceptable on March 3, 2023.

[b] McMillan, T. Label and Labeling Review for Tyenne (BLA 761275). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 FEB 08. TTT ID No.: 202.

3 RECOMMENDATIONS FOR FRESENIUS KABI

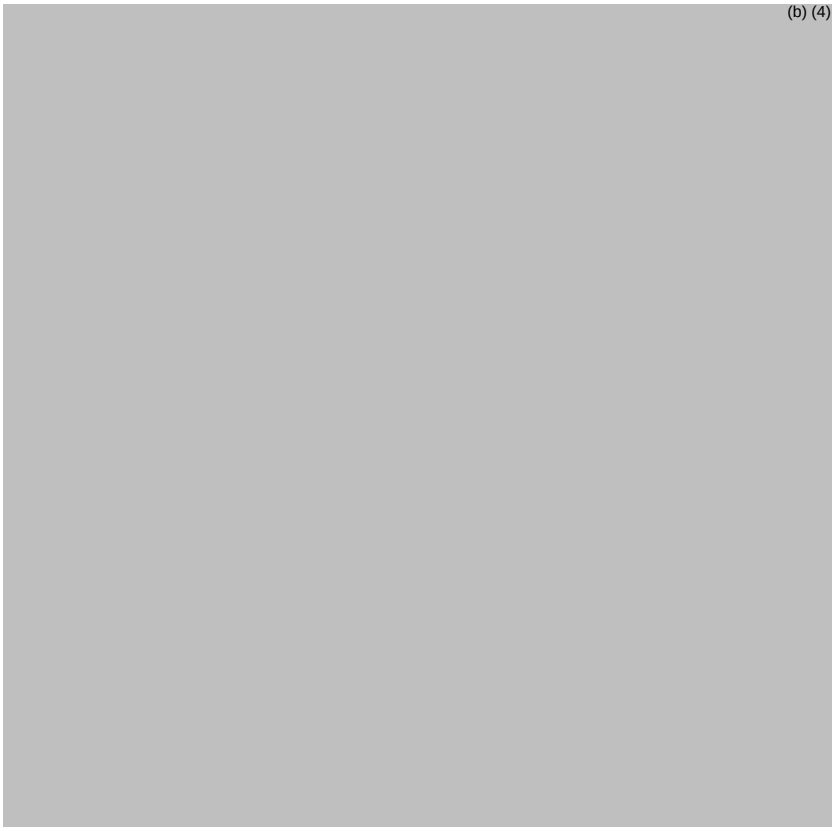
We recommend the following be implemented prior to approval of this BLA supplement:

A. An orange color is utilized for the 162 mg/0.9 mL autoinjector (AI) strength presentation and overlaps with the (b) (4) color utilized in the 400 mg/20 mL vial strength presentation. Overlap in the color scheme utilized between two different strengths may lead to selection medication errors. Utilize a different color blocking for the AI carton labeling and container label.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MARCH 21, 2023

Container labels and Carton labeling

Autoinjector



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/s/

TERESA S MCMILLAN
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IDALIA E RYCHLIK
03/30/2023 03:14:32 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 27, 2023

TO: Nikolay P. Nikolov, MD
Director
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Office of New Drugs

Nicholas Kozauer, MD
Director
Division of Neurology II
Office of Neuroscience
Office of New Drugs

FROM: Xikui Chen, Ph.D.
Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Kimberly A. Benson, Ph.D.
Deputy Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Routine inspection of Biokinetica S.A., Józefów, Poland

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of studies FKS456-002 (BLA 761275, tocilizumab biosimilar) Non-Responsive Non-Responsive conducted at Biokinetica S.A., Józefów, Poland.

Form FDA 483 was not issued. However, the following two items were discussed at the inspection close-out: (1) The laboratory did not always follow processing time instructions of centrifuging blood samples for 15 minutes, and (2) There was no documentation of a handoff of the investigational products from the pharmacy to clinic staff.

Based on the evaluation of the discussion items in section 3.1 in this review, the two discussion issues had no impact on data

integrity or subject safety. Therefore, I conclude that data from the audited studies FKS456-002 and Non-Responsive are reliable.

2. Inspected Studies:

Study Number: FKS456-002 (BLA 761275)
Study Title: "A randomized, double-blind, parallel-group, single dose study to compare the pharmacokinetics, safety, tolerability, and immunogenicity of intravenous administration of MSB11456 (proposed tocilizumab biosimilar) versus US-licensed Actemra® in healthy volunteers"
Clinical study conduct period: 9/24/2020 – 1/29/2021

Non-Responsive

3. Inspectional Findings

ORA investigator Tawny L. Colling inspected Biokinetica S.A., Józefów, Poland from October 17 to 21, 2022.

This was the first OSIS inspection of Biokinetica S.A. under the BA/BE program.

The current inspection included review of the subject screening and enrollment processes, training records, source documents, informed consent, ethics committee approvals, delegation logs, monitoring site visits, subject records, randomization and dosing documents, adverse events, test article accountability, blood centrifugation records, and study protocol and amendments. No sample was collected, and no refusals were encountered.

At the conclusion of the inspection, investigator Colling did not issue Form FDA 483 to the clinical site. There were two discussion items presented to the firm at the close-out meeting.

My evaluation of the discussion items is presented below.

3.1. Discussion Items

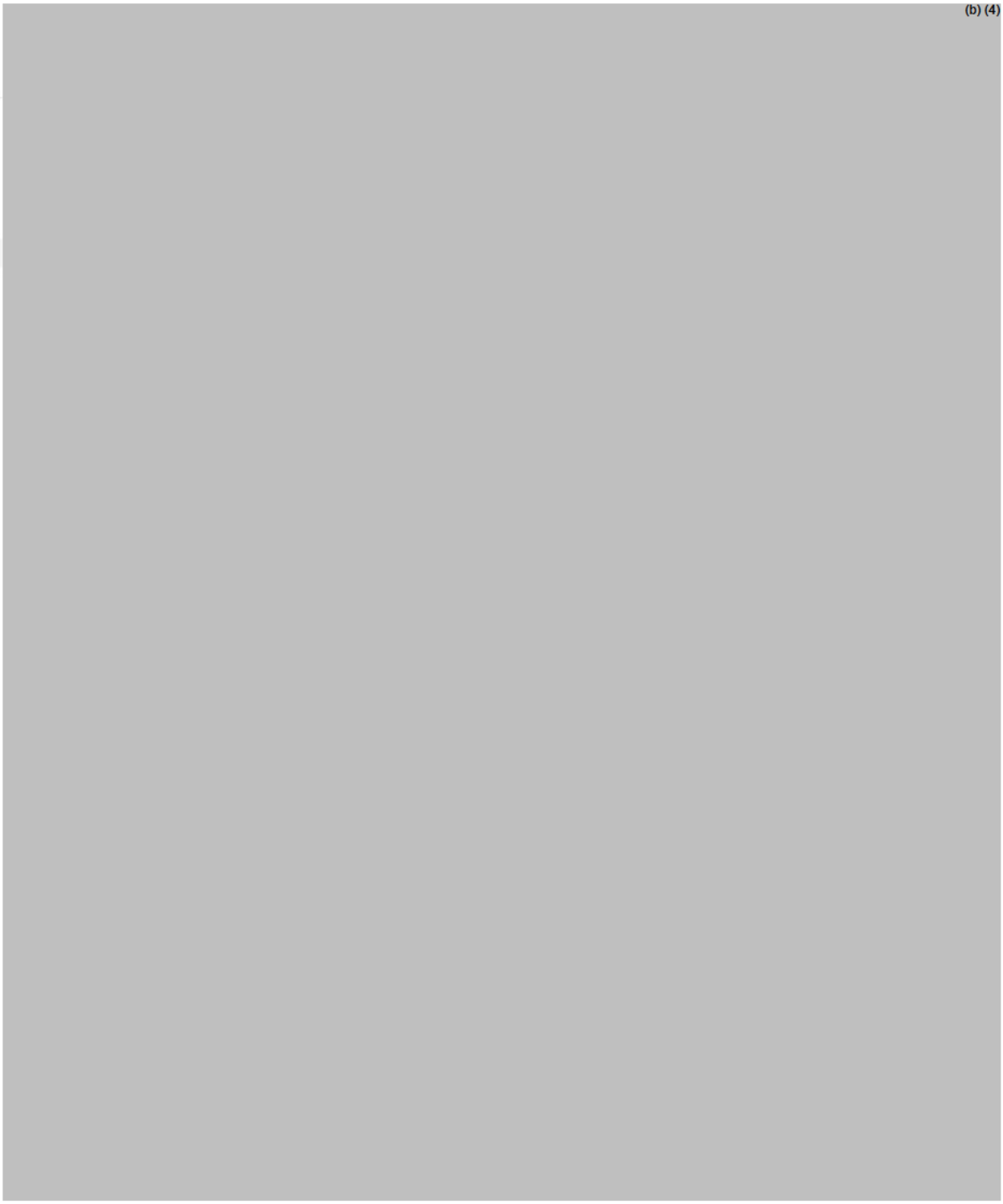
3.1.1. Item 1

The protocol for study FKS456-002 required that the blood samples be centrifuged for 15 minutes. The following discrepancies were observed:

Subject (b) (6)'s 24h PK sample was centrifuged for 11 minutes, starting at 10:10 and ending at 10:21. Subject (b) (6)'s 48h PK sample was centrifuged for 10 minutes, starting at 07:55 and ending at 08:05.

OSIS Evaluation:

In fact (below), the attachment 16.1.10 to the protocol called for centrifuging blood in Serum Separator Tubes for 10 minutes. The discussion item was not true in fact. This item has no adverse effect on data integrity.



3.1.2. Item 2

There was no documentation of a handoff of the investigational products (IP) from the pharmacy to clinic staff.

OSIS Evaluation:

There should be documentation of transferring IP from the pharmacy to clinic personnel. However, as the audited studies were randomized and double-blind, this item has no adverse effect on study outcomes.

3.2. Specific concerns from OND (if applicable)

Not applicable.

cc: OTS/OSIS/Kassim/Folian/Pham/Yu/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Benson/Skelly/Au/Ou/Chen
ORA/OMPTO/OBIMO/FDAInternational BIMO@fda.hhs.gov
ORA/OMPTO/OBIMO/Colling

ECMS Link:
http://ecmsweb.fda.gov/webtop/drl/objectId/0b0026f88759043f

OSIS File #: Non-Responsive; BE9585 (BLA 761275)
eNSpect Operation ID #: 228269
Draft: XC 02/23/2023
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XIKUI CHEN
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02/27/2023 02:01:39 PM

KIMBERLY A BENSON
02/27/2023 02:40:33 PM

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:	February 8, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761275
Product Name and Strength:	Tyenne (tocilizumab-XXXX)[a] Injection, 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL), 162 mg/0.9 mL
Applicant/Sponsor Name:	Fresenius Kabi
OSE RCM #:	2022-2098-02
DMEPA 1 Safety Evaluator:	Teresa McMillan, PharmD
DMEPA 1 Team Leader:	Idalia Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on February 6, 2023 for Tyenne. Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container label and carton labeling for Tyenne (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

The revised prefilled syringe and autoinjector container labels and carton labeling are acceptable from a medication error perspective. However, the revised vial container labels and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide recommendations in Section 3 for Fresenius Kabi.

[a] The proposed proprietary name, Tyenne was found conditionally acceptable on November 30, 2022. The nonproprietary name has not yet been determined; therefore, the placeholder, tocilizumab-xxxx, is used throughout this review to refer to the nonproprietary name for this product.

[b] McMillan, T. Label and Labeling Review for Tyenne (BLA 761275). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JAN 19. RCM No.: 2022-2098-01.

3 RECOMMENDATIONS FOR FRESENIUS KABI

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

1. Similar color blocking is used for the 80 mg/4 mL (light blue) and the 200 mg/10mL ([(b) (4)]) strength vials. The selection of colors do not adequately differentiate these strengths and the lack of differentiation may contribute to selection medication errors. Consider the use of distinctly different colors, boxing, or some other means to provide adequate differentiation between the vial container labels and carton labeling.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 6, 2023

Container labels and Carton labeling

Autoinjector

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/s/

TERESA S MCMILLAN
02/08/2023 06:38:30 PM

IDALIA E RYCHLIK
02/09/2023 12:15:30 PM

Clinical Inspection Summary

Date	February 8, 2023
From	Tina Chang, M.D., Medical Officer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Eric Gapud, M.D., Clinical Reviewer Rachel Glaser, M.D., Associate Director for Therapeutic Review Susie Choi, PharmD, Regulatory Project Manager Division of Rheumatology and Transplant Medicine (DRTM)
BLA #	761275
Applicant	Fresenius Kabi USA, LLC
Drug	MSB11456 (tocilizumab biosimilar-xxxx)
NME (Yes/No)	No
Proposed Indication(s)	Treatment of Rheumatoid Arthritis (RA): Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs)
Consultation Request Date	July 20, 2022
Summary Goal Date	April 30, 2023
Action Goal Date	May 31, 2023
BsUFA Date	May 31, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Maria Misterska-Skora and Anna Zubrzycka-Sienkiewicz were inspected in support of BLA 761275 covering one clinical study FKS456-001. Despite some minor protocol deviations and data entry errors, the study appears to have been conducted adequately, and the data generated by these clinical investigator (CI) sites appear acceptable in support of this BLA.

II. BACKGROUND

BLA 761275 was submitted in support of the use of MSB11456 (tocilizumab biosimilar-xxxx) as a biosimilar to RoActemra (tocilizumab) for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs). The proposed indication for MSB11456 is intended to be the same as that of RoActemra. MSB11456 is a recombinant humanized monoclonal immunoglobulin subtype G1 antibody to interleukin-6 receptors. The sponsor submitted a single Phase 3 study to support this BLA. The following briefly describes the protocol:

FKS456-001, "A Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Two-Arm

Study to Evaluate the Efficacy, Safety and Immunogenicity of MSB11456 Compared to European Union-approved RoActemra in Patients with Moderately to Severely Active Rheumatoid Arthritis (APTURA I study)."

Protocol FKS456-001 was a Phase 3, randomized, double-blind, active-controlled, multiple fixed dose, parallel-group study to compare efficacy and safety of the biosimilar MSB11456 versus European Union-approved RoActemra (EU-RoActemra). The primary objective was to demonstrate equivalent efficacy of proposed biosimilar tocilizumab MSB11456 and EU-approved RoActemra both administered subcutaneously to patients with moderately to severely active rheumatoid arthritis.

Sites: The study was conducted at 81 sites in Europe (Bulgaria, Czech Republic, Georgia, Hungary, Moldova, Poland, Russia, Serbia, and Slovakia).

Subjects: *A total* of 604 subjects were randomized (i.e., 302 subjects received MSB11456 and 302 received RoActemra). There were 543 subjects who completed the study to Week 30 (i.e., 267 subjects who received MSB11456 and 276 who received RoActemra).

Study initiation and completion dates: August 3, 2020 (first patient, first visit); October 11, 2021 (last patient, last visit completing Week 30)

Week 30 data cutoff date: October 11, 2021

The total study duration was 67 weeks. The study included a Screening Period of up to 28 days, a double-blind 24-week core treatment period, an additional 28-week double-blind extended treatment period (Week 24 to 52), and a 12-week safety evaluation period. A safety follow-up visit (Week 55) was to be performed four weeks after the last dose of the study drug.

During the 24-week core treatment period, subjects were randomized (1:1) to receive 162 mg of MSB 11456 or EU-RoActemra via subcutaneous injection starting at Day 1, then weekly up to Week 51. The first three doses (Day 1, Day 8, and Day 15) were administered on site to ensure the subject was appropriately trained. In the extended treatment period, subjects who had received RoActemra were to be re-randomized 1:1 to continue RoActemra or switch to MSB 11456. Subjects that were originally randomized to MSB11456 were to continue this treatment for the complete 52 weeks of treatment. All subjects were to continue taking their stable dose of methotrexate during the treatment period of the study.

Main inclusion criteria included male and female subjects ≥18 years of age with moderately to severely active RA who have had an inadequate response to ≥1 disease-modifying anti-rheumatic drug(s) which may include biologic disease-modifying anti-rheumatic drugs and who are currently receiving a stable dose of methotrexate. Please see protocol for full inclusion and exclusion criteria.

Primary Efficacy Endpoint: The mean absolute change from baseline in Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR) to Week 24.

The primary efficacy analysis at Week 24 was conducted after all subjects had completed the Week 30 assessments.

The DAS28-ESR is a composite endpoint made up of the following components:
• Tender Joint Count (28 joints)
• Swollen Joint Count (28 joints)
• Patient's Global Assessment of Disease Activity (scale of 0-100)
• Erythrocyte sedimentation rate

The 28 joints to be assessed for DAS28 include the following:
• Shoulders
• Elbows
• Wrists
• Interphalangeal on digit 1
• Proximal interphalangeal joints on digits 2 - 5
• Metacarpophalangeal joints on digits 1 - 5
• Knees

Rationale for Site Selection

The CIs Drs. Anna Zubrzycka-Sienkiewicz (Site #2507) and Maria Misterska-Skora (Site #2519) were selected for GCP inspections based on number of enrolled subjects and the fact that these CI sites were the top two sites with the greatest influence on the primary efficacy results.

III. RESULTS (by site):

1. **Dr. Anna Zubrzycka-Sienkiewicz**
   Site #2507
   333 Aleja Wilanowska Street
   Warsaw, Poland
   Inspection Dates: October 17-20, 2022

At this site, 30 subjects were screened, 21 subjects were randomized, and 19 subjects completed the study through Week 24. Two subjects withdrew due to adverse events. Subject (b) (6) (randomized to MSB11456) withdrew due to lumbar spinal stenosis that required surgery, and Subject (b) (6) (randomized to MSB11456) withdrew due to elevated bilirubin level.

Records were reviewed for all 21 randomized subjects. Records reviewed included, but were not limited to, protocol versions, ethics committee oversight, informed consent, eligibility, protocol adherence, concomitant medications, financial disclosures, adverse events, test article accountability, adverse event reporting, protocol deviations, and primary efficacy endpoint source records. All source records were in paper format.

The components of the primary efficacy endpoint data for the DAS28-ESR at baseline and Week 24, as documented in the source records, were compared with the data line listings provided by the sponsor. No discrepancies were noted. There was no evidence of underreporting of adverse events or of unreported protocol deviations.

2. **Dr. Maria Misterska-Skora**
   Site #2519
   Ul. Ludwika Solskiego 4a/1
   Centrum Medyczne Oporow
   Wroclaw, Poland
   Inspection dates: October 24-28, 2022

At this site, 32 subjects were screened, 21 subjects were randomized, and 20 subjects completed the study through Week 20. Subject (b) (6) (randomized to MSB11456) withdrew due to elevated bilirubin levels.

Source documents were reviewed for all 21 randomized subjects. Records reviewed included, but were not limited to, protocol versions, ethics committee oversight, informed consent, eligibility, protocol adherence, concomitant medications, financial disclosures, adverse events, test article accountability, adverse event reporting, protocol deviations, and primary efficacy endpoint source records. All source records were in paper format.

The components of the primary efficacy endpoint data for the DAS28-ESR at baseline and Week 24, as documented in the source records, were compared with the data line listings provided by the sponsor. There were two instances in which the tender joint counts reported in the source records was not the same as the results provided in the sponsor data line listing. The source record for Subject (b) (6) (randomized to MSB11456) reported 21 tender joints at Baseline, but the EDC and sponsor line listing reported 18 tender joints at Baseline. The source record for Subject (b) (6) (randomized to MSB11456) reported 0 tender joints at Week 24, but the EDC and sponsor line listing reported 4 tender joints at Week 24. Except for a subject with a “common cold,” there was no evidence of underreporting of adverse events.

Reviewer’s comment: Both discrepancies would not have favored study drug as these changes would result in less of a change in disease activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR).

The protocol v.2 dated 5/6/20 states under Section 7.8 Imaging that a bidirectional chest X-ray (CXR) obtained within 3 months prior to randomization will be used to determine eligibility. If patients do not have a bidirectional chest X-ray available within 3 months of randomization, a bidirectional chest X-ray must be done prior to randomization to evaluate for any malignant process, ongoing infectious disease, or of an inactive (latent) tuberculosis. Subjects (b) (6), (b) (6) only had an AP view of CXR.

Reviewer's comment: The CXR reports that were performed had no evidence of malignancy, infectious disease or TB lesions, and there was a negative QuantiFERON test for every subject prior to enrollment. There was no evidence of subject harm.

{See appended electronic signature page}

Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/

OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
OSI/Database PM/

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02/08/2023 01:57:51 PM

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:	January 19, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761275
Product Name and Strength:	Tyenne ((tocilizumab-XXXX)[a] Injection, 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL), 162 mg/0.9 mL
Applicant/Sponsor Name:	Fresenius Kabi
OSE RCM #:	2022-2098-01
DMEPA 1 Safety Evaluator:	Teresa McMillan, PharmD
DMEPA 1 Team Leader:	Idalia Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on December 27, 2022 for Tyenne. Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container labels and carton labeling for Tyenne (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

The revised container and carton labeling is unacceptable from a medication error perspective. We provide recommendations in Section 3 for Fresenius Kabi.

[a] The proposed proprietary name, Tyenne was found conditionally acceptable on November 30, 2022. The nonproprietary name has not yet been determined; therefore, the placeholder, tocilizumab-xxxx, is used throughout this review to refer to the nonproprietary name for this product.

[b] McMillan, T. Label and Labeling Review for Tyenne (BLA 761275). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 DEC 15. RCM No.: 2022-2098.

3 RECOMMENDATIONS FOR FRESENIUS KABI

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

A. The container labels and carton labeling are not adequately differentiated to minimize selection errors between the proposed prefilled syringe, autoinjector, and vial presentations. We note that you have used color blocking of the strength instead of differentiating by presentation. In addition, you have proposed to overlap the "(b) (4)" color for the vial and autoinjector. These proposed revisions are inadequate to minimize medication selection errors. We are aware of reported medication selection errors with prefilled pens/autoinjectors and prefilled syringes as reported by ISMP.[c] These errors may result in a delay in therapy or the user's inability to operate the device. Therefore, it is recommended all presentations labels/labeling are clearly differentiated from each other to minimize medication selection errors. Consider the use of different colors, boxing, or some other means to provide adequate differentiation between all proposed presentations.

[c] Community/Ambulatory Care ISMP Medication Safety Alert: "Look-alike cartons: Potential for wrong specialty product to be dispensed". FEBRUARY 2002: VOLUME 21: ISSUE 2.

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

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON DECEMBER 27, 2022

Container labels and Carton labeling

Autoinjector

(b) (4)

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TERESA S MCMILLAN
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IDALIA E RYCHLIK
01/19/2023 12:49:09 PM

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:	December 15, 2022
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761275
Product Name, Dosage Form, and Strength:	Tyenne (tocilizumab-XXXX)[a] Injection, 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL), 162 mg/0.9 mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Fresenius Kabi
FDA Received Date:	May 31, 2022 and October 12, 2022
TTT ID #:	2022-2098
DMEPA 1 Safety Evaluator:	Teresa McMillan, PharmD
DMEPA 1 Team Leader:	Idalia Rychlik, PharmD

[a] The proposed proprietary name, Tyenne was found conditionally acceptable on November 30, 2022. The nonproprietary name has not yet been determined; therefore, the placeholder, tocilizumab-xxxx, is used throughout this review to refer to the nonproprietary name for this product.

1 REASON FOR REVIEW

As part of the approval process for Tyenne (tocilizumab-XXXX) Injection, the Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the proposed Tyenne Prescribing Information (PI), Instructions for Use (IFU), Medication Guide (MG), carton labeling, and container labels for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling 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 AND RECOMMENDATIONS

The proposed prescribing information, Medication Guide, and Instructions for Use did not identify areas of vulnerability that may lead to medication error. However, the container labels and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for Fresenius Kabi. 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 FRESENIUS KABI

Table 2. Identified Issues and Recommendations for Fresenius Kabi (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The format for the expiration date and lot number is not defined.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors. Clearly defining the lot number is needed for product line identification.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. Ensure the lot number is clearly differentiated from the expiration date.
2.	There is a highly similar alignment between the label and labeling layout, strength color schemes and trade dress between the proposed product	Similar alignment of label and labeling layout, color choice and trade dress across product lines may lead to selection errors.	Develop a unique design approach across each product line to minimize selection errors.

Table 2. Identified Issues and Recommendations for Fresenius Kabi (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	and that utilized in your Idacio product line.		
3.	The barcode has been omitted from the prefilled syringe container label and the vial carton labeling.	Missing important information such as the barcode may lead to the inability to accurately verify the intended drug.	Place a scannable barcode on all individual container labels. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each individual container label as required per 21CFR 201.25(c)(2).
4.	There is a QR code present on all of the carton labeling presentations that states, "SCAN FOR ADDITIONAL INFORMATION".	The additional information that is contained within the QR code wasn't defined and may lead to confusion.	Clarify what additional information the QR code contains once scanned.
5.	The placeholder term "TRADENAME" is used throughout the labels and labeling,	The conditionally approved proprietary name, Tyenne, should be used throughout the labels and labeling to minimize confusion.	Replace all instances of "TRADENAME" to the conditionally approved proprietary name 'Tyenne" throughout the labels and labeling.
Container Label(s)			
1.	The dosage form statement is missing from the principal display panel of some of the container labels.	Missing important dosage form information may lead to confusion.	Place the dosage form statement, "Injection" directly beneath the proper name and place the proper name in parenthesis.

Table 2. Identified Issues and Recommendations for Fresenius Kabi (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The image of the autoinjector and the prefilled syringe on the container blister labels lacks prominence.	Lack of prominence of these images may lead to selection errors.	Increase the prominence of the autoinjector and prefilled syringe images. Consider relocating image to a more prominent location on the label such as directly below the strength statement.
3.	The vial container label route of administration statement differs from the route of administration presented on the carton labeling.	Inconsistency of the route of administration across the labels and labeling may lead to wrong route medication errors and confusion.	For consistency, revise the route of administration statement to read as follows: For Intravenous Infusion Only After Dilution
Carton Labeling			
1.	The recommended dosage statement is inconsistent with the Prescribing Information.	Inconsistency with the prescribing information may lead to dosing and administration medication errors.	To ensure consistency with the Prescribing Information, Revise "(b) (4) to read "Recommended Dosage: See Prescribing Information."
2.	The layout of important statements on principal display panel of the prefilled syringe, autoinjector, and vial carton labeling can be improved for clarity of information.	Important information that isn't displayed properly can be easily overlooked and lead to confusion.	• Relocating the strength statements directly under the term 'Injection': • Revise Discard Unused Portion and single dose vial to read Single Dose Vial– Discard Unused Portion all on one line.
3.	The prefilled syringe and autoinjector carton labeling are not clearly differentiated.	Lack of adequate differentiation may contribute to selection errors	Consider the use of different colors, boxing, or some other means to provide adequate differentiation between the

Table 2. Identified Issues and Recommendations for Fresenius Kabi (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			prefilled syringe and autoinjector container labels.

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.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Tyenne that Fresenius Kabi submitted on. May 31, 2022.

Table 3. Relevant Product Information for Tyenne	
Initial Approval Date	N/A
Nonproprietary name	tocilizumab-XXXX
Indication	Rheumatoid Arthritis (RA) • Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs). Giant Cell Arteritis (GCA) • Adult patients with giant cell arteritis. Polyarticular Juvenile Idiopathic Arthritis (PJIA) • Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis (SJIA) • Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.
Route of Administration	Intravenous and Subcutaneous
Dosage Form	Injection
Strength	80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL), 162 mg/0.9 mL
Dose and Frequency	Rheumatoid Arthritis Recommended Adult Intravenous Dosage: When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.

Recommended Adult Subcutaneous Dosage:

Patients less than 100 kg weight	162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response
Patients at or above 100 kg weight	162 mg administered subcutaneously every week

Giant Cell Arteritis

Recommended Adult Intravenous Dosage:

The recommended dose is 6 mg per kg every 4 weeks in combination with a tapering course of glucocorticoids. TRADENAME can be used alone following discontinuation of glucocorticoids.

The recommended dose is 162 mg given once every week as a subcutaneous injection, in combination with a tapering course of glucocorticoids.

A dose of 162 mg given once every other week as a subcutaneous injection, in combination with a tapering course of glucocorticoids, may be prescribed based on clinical considerations.

TRADENAME can be used alone following discontinuation of glucocorticoids.

Polyarticular Juvenile Idiopathic Arthritis

Recommended Intravenous PJIA Dosage Every 4 Weeks	
Patients less than 30 kg weight	10 mg per kg
Patients at or above 30 kg weight	8 mg per kg

	<table><tr><td colspan="2">Recommended Subcutaneous PJIA Dosage</td></tr><tr><td>Patients less than 30 kg weight</td><td>162 mg once every three weeks</td></tr><tr><td>Patients at or above 30 kg weight</td><td>162 mg once every two weeks</td></tr></table> Systemic Juvenile Idiopathic Arthritis <table><tr><td colspan="2">Recommended Intravenous SJIA Dosage Every 2 Weeks</td></tr><tr><td>Patients less than 30 kg weight</td><td>12 mg per kg</td></tr><tr><td>Patients at or above 30 kg weight</td><td>8 mg per kg</td></tr></table> <table><tr><td colspan="2">Recommended Subcutaneous SJIA Dosage</td></tr><tr><td>Patients less than 30 kg weight</td><td>162 mg every two weeks</td></tr><tr><td>Patients at or above 30 kg weight</td><td>162 mg every week</td></tr></table>
How Supplied	TRADENAME (tocilizumab) injection is a preservative-free, sterile clear and colorless to pale yellow solution. The following packaging configurations are available:

	For Intravenous Infusion TRADENAME Single-Dose Vial Each TRADENAME carton contains one vial. Each vial is supplied as 80 mg/4 mL (NDC xxxxx-xxx-xx), 200 mg/10 mL (NDC xxxxx-xxx-xx), and 400 mg/20 mL (NDC xxxxx-xxx-xx) TRADENAME solution for further dilution prior to intravenous infusion. The vial stopper is (b) (4). *For Subcutaneous Injection* TRADENAME Prefilled Syringe Each TRADENAME carton contains (b) (4) a single-dose prefilled syringe delivering 162 mg/0.9 mL of TRADENAME. The syringe plunger stopper and needle cover are not made with natural rubber latex. The NDC number is xxxxx-xxx-xx. TRADENAME Autoinjector Each TRADENAME carton contains (b) (4) a single-dose autoinjector delivering 162 mg/0.9 mL of TRADENAME. The syringe plunger stopper and needle cover are (b) (4). The NDC number is xxxxx-xxx-xx.
Storage	Do not use beyond expiration date on the container, package, prefilled syringe, or autoinjector. TRADENAME must be refrigerated at 36°F to 46°F (2ºC to 8ºC). Do not freeze. A single prefilled syringe (or autoinjector) may be stored at (b) (4) 77°F (25°C) for a single period of up to 14 days. (b) (4). Protect the vials, syringes, and autoinjectors from light by storage in the original package until time of use, and keep syringes and autoinjectors dry.

APPENDIX B. PREVIOUS DMEPA REVIEWS-N/A

APPENDIX C. ISMP NEWSLETTERS-N/A

APPENDIX D. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)-N/A

APPENDIX E. N/A

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,[b] along with postmarket medication error data, we reviewed the following Tyenne labels and labeling submitted by Fresenius Kabi.

- Container label(s) received on May 31, 2022
- Carton labeling received on May 31, 2022
- Instructions for Use received on May 31, 2022 and October 12, 2022, available from \\CDSESUB1\EVSPROD\bla761275\0010\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-pfs.docx \\CDSESUB1\EVSPROD\bla761275\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-ai.docx
- Prescribing Information and Medication Guide received on May 31, 2022, available from \\CDSESUB1\EVSPROD\bla761275\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-and-medication-guide.docx

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

9 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

TERESA S MCMILLAN
12/15/2022 01:16:43 PM

IDALIA E RYCHLIK
12/15/2022 01:29:10 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 10/5/2022

TO: Division of Rheumatology and Transplant Medicine (DRTM)
Office of Immunology and Inflammation (OII)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 761275

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

OSIS conducted a Remote Regulatory Assessment (RRA) for the clinical site in NON-RESPONSIVE, which falls within the surveillance interval. The RRA was conducted under the following submission: BLA NON-RESPONSIVE. OSIS concluded that data from the reviewed study was reliable.

OSIS conducted a RRA for the analytical site in NON-RESPONSIVE, which falls within the surveillance interval. The RRA was conducted under the following submission: NDA NON-RESPONSIVE. OSIS observed the following objectionable condition:

- Failure to establish a procedure for reanalysis and reporting of incurred sample reproducibility (ISR) results

After review of the findings and the site's response, OSIS concluded that data from the reviewed studies was reliable. (OSIS Final Review – Sept 2021 RRA).

Sites

Facility Type	Facility Name	Facility Address
Clinical	Auckland Clinical Studies	Ground Floor, 3 Ferncroft Street, ACS House, Grafton, Auckland, New Zealand
Analytical		(b) (4)

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/s/

JAMES J LUMALCURI
10/05/2022 01:06:59 PM