

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761086Orig1s000

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: December 5, 2019

To: Sally Seymour, MD
Acting Director
**Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

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)

Kelly Jackson, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (nonproprietary name): AVSOLA (infliximab-axxq)

Dosage Form and Route: injection, for intravenous use

Application Type/Number: BLA 761086

Applicant: Amgen, Inc.

¹The proposed proprietary name, AVSOLA and the nonproprietary (proper) name, infliximab-axxq are conditionally acceptable, until such time as the application is approved.

1 INTRODUCTION

On December 14, 2018, Amgen, Inc. submitted for the Agency's review a Biologics License Application (BLA) for their product AVSOLA (infliximab-axxq) for injection, for intravenous use. The Applicant seeks approval for AVSOLA (infliximab-axxq) for injection, for intravenous use as a biosimilar product to the reference biologic product REMICADE (infliximab) Lyophilized Concentrate for Injection, for Intravenous Use, licensed under BLA 103772.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on February 15, 2019, for DMPP to review the Applicant's proposed Medication Guide (MG) for AVSOLA (infliximab-axxq) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft AVSOLA (infliximab-axxq) MG received on December 14, 2018, revised by the Review Division throughout the review cycle, and received by on August 28, 2019.
- Draft AVSOLA (infliximab-axxq) Prescribing Information (PI) received on December 14, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on August 28, 2019.
- Approved REMICADE (infliximab) comparator labeling dated June 19, 2018.

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%.

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. We reformatted the MG document using the Arial font, size 10.

In our review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KELLY D JACKSON
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MARCIA B WILLIAMS
12/05/2019 07:55:44 AM

LASHAWN M GRIFFITHS
12/05/2019 03:11:28 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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 5, 2019

Requesting Office or Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Application Type and Number: BLA 761086

Product Name and Strength: Avsola
(infliximab-axxq)
Injection
100 mg/vial

Applicant/Sponsor Name: Amgen, Inc.

OSE RCM #: 2018-2747-3

DMEPA Safety Evaluator: Teresa McMillan, PharmD

DMEPA Team Leader: Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on December 4, 2019 for Avsola. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the revised container label and carton labeling for Avsola (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.^a

2 CONCLUSION

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

^a McMillan T. Label and Labeling Review for Avsola (BLA 761086). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 22. RCM No.: 2018-2747-2.

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/s/

TERESA S MCMILLAN
12/05/2019 11:36:35 AM

IDALIA E RYCHLIK
12/05/2019 11:38:21 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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: November 22, 2019

Requesting Office or Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Application Type and Number: BLA 761086

Product Name and Strength: Avsola
(infliximab-axxq)
Injection,
100 mg/vial

Applicant/Sponsor Name: Amgen, Inc.

OSE RCM #: 2018-2747-2

DMEPA Safety Evaluator: Teresa McMillan, PharmD

DMEPA Team Leader: Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 12, 2019 for Avsola. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the revised container label and carton labeling for Avsola (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.^a

2 CONCLUSION

The revised carton labeling and container label are unacceptable from a medication error perspective. Below, we have provided recommendations in **Table 1** for Amgen.

^a McMillan T. Label and Labeling Review for Avsola(BLA 761086). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019OCT18. RCM No.: 2018-2747-1.

3 RECOMMENDATIONS FOR AMGEN, INC.

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

Table 1: Identified Issues and Recommendations for Amgen (entire table to be conveyed to Applicant)

Container Labels and Carton Labeling			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	You have proposed to utilize the following expiration date format: “MM/YY” and did not specify if you intend to use alphabetical or numerical characters to represent the month.	Lack of a defined expiration date may lead to deteriorated drug product errors and is needed in order that we assess it from a medication error perspective. Additionally, if alphabetical characters are used to represent the month they may be misunderstood because June/July and May/March contain the same first two letters (‘JU’ and ‘MA’). cause confusion	To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the 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.
2.	As proposed, the strength statement lacks prominence.	We acknowledge your rationale that the prominence of the quantity statement, “100 mg/vial” is also displayed in large font,	For all panels that display the strength statement we recommend the you move the strength statement directly

		<p>immediately to the left of the blue/green graphic. However, a strength graphic displayed on the side of the label and labeling does not replace the necessity of prominence for the strength statement on the primary display panel. 21 CFR 201.15(a)(6).</p>	<p>below the dosage form. Revise to the following:</p> <p>Proprietary name Proper name For injection 100 mg/vial For Intravenous Infusion Only</p>
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/s/

TERESA S MCMILLAN
11/22/2019 01:46:52 PM

IDALIA E RYCHLIK
11/22/2019 01:56:33 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

DATE: November 22, 2019

FROM: Sally Seymour, MD
Director, Division of Pulmonary, Allergy, and Rheumatology Products

SUBJECT: BLA 761086, submitted by Amgen Inc.

TO: BLA 761086, submitted by Amgen Inc.

Background

Under section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355c) (often referred to by the acronym of the legislation that created it, the Pediatric Research Equity Act (PREA)), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain assessments of the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective, unless this requirement is waived, deferred, or inapplicable.¹

On December 14, 2018, Amgen Inc. (Amgen or Applicant) submitted a Biologics License Application (BLA), BLA 761086, under section 351(k) of the Public Health Service Act (PHS Act) for a proposed biosimilar to US-licensed Remicade (US-Remicade) (BLA 103772), seeking licensure for the following indications:

¹ The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) added section 351(k) to the Public Health Service Act (PHS Act) and amended section 505B of the FD&C Act. With respect to the latter, it specified that PREA is applicable to a biosimilar product that has not been determined to be interchangeable with a reference product (see section 7002(a), (d)(2) of the BPCI Act). With respect to the former, an application under section 351(k) of the PHS Act must include, among other things, information demonstrating that “the condition or conditions of use prescribed, recommended, or suggested in the labeling for the proposed biological product have been previously approved for the reference product” and “the route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product” (section 351(k)(2)(A)(i)(III)-(IV) of the PHS Act).

- *Crohn's Disease*:
 - reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
 - reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease.
- *Pediatric Crohn's Disease*: reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- *Ulcerative Colitis*: reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- *Pediatric Ulcerative Colitis*: reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- *Rheumatoid Arthritis in combination with methotrexate*: reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active disease.
- *Ankylosing Spondylitis*: reducing signs and symptoms in patients with active disease.
- *Psoriatic Arthritis*: reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.
- *Plaque Psoriasis*: treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

Discussion

US-Remicade was licensed for treatment of adults with Crohn's Disease on August 24, 1998 (see also actions dated June 18, 2002, and April 1, 2003).² As described in the August 24, 1998, approval letter, the applicant agreed to conduct a clinical trial in pediatric patients with Crohn's disease to determine the consistency of benefits with those observed in adults.³ US-Remicade fulfilled this commitment on May 19, 2006. Additionally, US-Remicade was orphan designated for pediatric Crohn's disease on November 11, 2003. US-Remicade was licensed for pediatric Crohn's disease in patients 6 years of age and older on May 19, 2006.⁴

² FDA approved the BLA for the Crohn's disease indication under the regulations for accelerated approval of biological products for serious or life-threatening illnesses (21 CFR 601 Subpart E). In the June 18, 2002 approval letter, FDA acknowledged the fulfillment of the applicant's commitment made under 21 CFR 601.42 to complete a randomized, double-blind, placebo-controlled clinical study(s) to evaluate safety and efficacy of continued use of infliximab for maintaining a sustained clinical outcome in patients with moderately to severely active Crohn's disease. The April 1, 2003 approval fulfilled the commitment to conduct a randomized, double-blind, placebo-controlled clinical study to evaluate safety and efficacy of continued use of infliximab for maintaining a sustained clinical outcome in patients with draining enterocutaneous fistula(s).

³ US-Remicade was licensed for Crohn's disease in adults prior to the enactment to PREA. In a 2002 decision, the U.S. District Court for the District of Columbia found the Pediatric Rule to be invalid and enjoined FDA from enforcing the rule. See *Ass'n of Am. Physicians & Surgeons, Inc. v. U.S. F.D.A.*, 226 F. Supp.2d. 204 (D.D.C. 2002).

⁴ See Orphan Drug Designations and Approvals database.

On November 10, 1999, FDA licensed US-Remicade for the treatment of adults with rheumatoid arthritis in combination with methotrexate. As described in the November 10, 1999, approval letter, the applicant agreed to conduct a juvenile rheumatoid arthritis clinical study.⁵ US-Remicade fulfilled this commitment on April 19, 2007.

On December 17, 2004, FDA licensed US-Remicade for the treatment of adults with ankylosing spondylitis and waived the pediatric study requirement. FDA licensed US-Remicade for the treatment of adults with psoriatic arthritis on May 13, 2005, and waived the pediatric study requirement. On September 26, 2006, FDA licensed US-Remicade for the treatment of adults with plaque psoriasis and waived the pediatric study requirement.

US-Remicade was orphan designated for the treatment of pediatric ulcerative colitis on November 12, 2003.⁴ FDA licensed US-Remicade for the treatment of adult ulcerative colitis on September 15, 2005⁶ and for the treatment of pediatric ulcerative colitis in patients 6 years and older on September 23, 2011. Because this indication had orphan designation, the sponsor was exempt from PREA.⁷

To date, US-Remicade is not licensed for the treatment of (and there is no age-appropriate formulation for these relevant pediatric populations):

- Juvenile rheumatoid arthritis in 0 to less than 4 years of age;⁸
- Psoriatic arthritis in pediatric patients;
- Ankylosing spondylitis in pediatric patients;
- Crohn's disease in 0 to less than 6 years of age;
- Ulcerative colitis in 0 to less than 6 years of age; and
- Plaque psoriasis in pediatric patients.

As described above, the requirements of PREA either were waived for or do not apply to US-Remicade for the above-described indications. Additionally, US-Remicade is not licensed for pediatric use in those above-described indications and does not have an age-appropriate formulation for those relevant pediatric populations. Applying the requirements of PREA to Avsola for these indications could result in Amgen seeking licensure for a condition of use for Avsola that has not been previously approved for US-Remicade and for which US-Remicade is not required to conduct pediatric assessments under PREA. The Agency has determined at this time that, with respect to the above-described indications, the requirements of PREA are not applicable to Amgen's December 14, 2018 BLA for Avsola. This determination is based on reading section 351(k) of the PHS Act, including section 351(k)(2)(A)(i)(III) and (IV), together with PREA's requirement for sponsors to conduct pediatric assessments and develop age-

⁵ US-Remicade was licensed for treatment of adults with rheumatoid arthritis in combination with methotrexate prior to the enactment to PREA. See note 3.

⁶ The agency originally deferred pediatric studies for ulcerative colitis. However, in a September 14, 2011 letter to the applicant, the agency clarified that since US-Remicade received orphan designation for the treatment of pediatric ulcerative colitis, PREA did not apply pursuant to section 505B(k) of the FD&C Act.

⁷ See Section 505B(k)(1) of the FD&C Act; at the time of the exemption, the relevant provision was codified at section 505B(k).

⁸ US-Remicade is also not licensed for juvenile rheumatoid arthritis in patients ages 4 to 17. The applicant is fulfilling its PREA requirements with respect to this age range by including relevant pediatric information in its labeling.

appropriate formulations for relevant pediatric populations. In this case, the reference product currently is not required to conduct pediatric assessments under PREA for the above-described indications, the reference product currently is not licensed for pediatric use for either all or certain pediatric populations in those indications, and the reference product currently does not have an age-appropriate formulation for relevant pediatric populations. Accordingly, we consider the requirements of PREA for Avsola with respect to the above-described indications to have been circumscribed by section 351(k).

Nothing in this memorandum forecloses FDA from, as appropriate, taking any additional steps within its authority to assure that pediatric use information is included in Avsola labeling, such as invoking the “marketed drugs” provision under PREA (section 505B(b) of the FD&C Act), in certain circumstances, in order to require sponsors to conduct pediatric assessments, or to take other appropriate steps, to support pediatric labeling for both the biosimilar product and the reference product.

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/s/

CHRISTINE H FORD
11/22/2019 11:39:13 AM

SALLY M SEYMOUR
11/22/2019 11:42:47 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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:	October 18, 2019
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761086
Product Name, Dosage Form, and Strength:	Avsola ^a (infliximab-axxq) For Injection 100 mg/vial Single Ingredient Product
Applicant/Sponsor Name:	Amgen, Inc.
OSE RCM #:	2018-2747-1
DMEPA Safety Evaluator:	Teresa McMillan, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted the revised, carton labeling, and container label received on September 13, 2019 for Avsola. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the revised carton labeling and container label for Avsola (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^b

^a The proposed proprietary name Avsola and the nonproprietary name infliximab-axxq were found conditionally acceptable for BLA 761086 on February 21, 2019 and March 1, 2019 respectively.

^b McMillan T. Label and Labeling Review for Avsola (BLA 761086). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 28. RCM No.:2018-2747.

2 CONCLUSION

The revised carton labeling and container label are unacceptable from a medication error perspective. Below, we have provided recommendations in **Table 1** for Amgen.

3 RECOMMENDATIONS FOR AMGEN, INC.

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

Table 3: Identified Issues and Recommendations for Amgen (entire table to be conveyed to Applicant)

Container Labels and Carton Labeling			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The expiration date format is not defined.	Lack of a defined expiration date may lead to deteriorated drug product errors and is needed in order that we assess it from a medication error perspective.	As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the 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.
Carton Labeling			
1.	The blue/green graphic is competing in prominence with other pertinent information such as the dosage form, route of administration, and strength.	Decreasing the prominence of the graphic or deleting it helps minimize the risk of dosing and administration errors.	<p>For all panels that display the blue/green graphic, decrease the prominence of or remove the graphic to allow prominence of more important information. Revise to the following:</p> <p>Proprietary name Proper name For injection 100 mg/vial For Intravenous Infusion Only</p> <p>Refer to FDA Draft Guidance For Industry: <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.</i> Draft Guidance: Container and Carton</p>
2.	The Recommended Dose statement is presented differently on multiple panels.	Consistent presentation of the recommended dose statement helps minimize dosing and administration errors.	<p>Present the Recommended Dosage statement on the side panel which has the following statement ensuring to include : “Reconstitute each vial with 10 mL Sterile Water for Injection, USP”</p> <p>Revise to the following (note the inclusion of the “Do NOT shake reconstituted solution” statement): Recommended Dosage: See prescribing information.</p>

			<p>Reconstitute each vial with 10 mL Sterile Water for Injection, USP. Do NOT shake reconstituted solution. Must further dilute with 0.9% Sodium Chloride Injection, USP.</p> <p>Once reconstituted, each mL contains 10 mg infliximab-axxq, dibasic sodium phosphate, anhydrous (0.49 mg), monobasic sodium phosphate, monohydrate (0.22 mg), polysorbate 80 (0.05 mg), and sucrose (50 mg).”</p> <p>The alphabetical order of the inactive ingredients is consistent with the prescribing information.</p> <p>If space is limited, remove or decrease the prominence of the blue/green graphic to allow room for this important information.</p>
3.	As presented, the principal display panel appears cluttered and crowded.	Crowded or cluttered labeling can contribute to important information being overlooked.	<p>Ensure there is adequate white space between the dosage form and the Single-Dose Vial. Discard unused portion statements as well as the net quantity statement.</p> <p>In addition, relocate the storage statement to the side/back panel that contains the reconstitution information ensuring there is adequate white space between each statement:</p>

			<p>Store refrigerated at 2°C to 8°C (36°F to 46°F) in the carton to Protect from Light. Unopened vials may also be stored at temperatures up to a maximum of 30°C (86°F) for a single period of up to 6 months. If stored under these conditions discard after ___/___/___.</p> <p>If space is limited, remove or decrease the prominence of the blue/green graphic to allow room for this important information.</p>
Container Label			
1.	The Recommended Dosage statement does not utilize consistent language as in the Prescribing Information.	Consistency of the recommended dosage statement helps to minimize dosing and administration errors.	Revise to the following: Recommended Dosage: See Prescribing Information
2.	The strength has been omitted.	Inclusion of the strength helps to minimize dosing errors.	Revise to the following: Proprietary name Proper name For injection 100 mg/vial For Intravenous Infusion Only

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/s/

TERESA S MCMILLAN
10/18/2019 04:07:25 PM

IDALIA E RYCHLIK
10/18/2019 04:09:17 PM

MEMORANDUM

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

DATE: October 11, 2019

TO: Sally Seymour, MD
Division Director
Division of Pulmonary, Allergy and Rheumatology
Products (DPARP)
Office of Drug Evaluation II (ODEII)
Office of New Drugs

AND

Ann T. Farrell, MD
Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs

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

AND

Xingfang Li, MD, RAC
Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Deputy Director
DGDSI, OSIS

SUBJECT: Routine inspection of CMAX, Adelaide, Australia,
supporting clinical study 20140108 (BLA 761086)

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of CMAX Clinical Research Pty Ltd, Adelaide, South Australia, Australia.

No objectionable conditions were observed and Form FDA 483 was not issued at the close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

After reviewing the inspectional findings, I conclude the data from the audited study 20140108 (BLA 761086) are reliable to support a regulatory decision, after excluding data from subjects [REDACTED] (b) (6).

2 Inspected Study:

BLA 761086

Study Number: 20140108

Study Title: "A Randomized, Single-blind, Single-dose 3-arm, Parallel Group Study to Determine the Pharmacokinetic Similarity of ABP 710 and Infliximab (Remicade®) in Healthy Adult Subjects"

Dates of conduct: November 2014 to February 2015

Clinical site: CMAX
(A division of Institute of Drug Technology (IDT), Australia Limited)
Level 5, East Wing
Royal Adelaide Hospital North Terrace,
Adelaide, South Australia, 5000 Australia

ORA investigator Andrace Deyampert (DET-DO) inspected CMAX, Adelaide, South Australia, Australia from August 12 to 16, 2019.

The current inspection covered standard operating procedures, protocol adherence, data verification, informed consent process/documentation, safety reporting, ethic committee approvals, monitoring, protocol deviations, subject screening, subject eligibility, product accountability and storage, and study personnel training.

3 Inspectional Findings

At the conclusion of the inspection, investigator Deyampert did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site.

However, during the inspection close out meeting, discussion items were reviewed with the CEO, Jane E. Kelly and study team,

including source documentation, quality assurance, and informed consent elements.

There were no voluntary corrections for the previous inspection given that the firm no longer has an analytical facility.

Discussion Item 1:

The source record of the electrocardiogram (EKG) for subject (b) (6) had an automatic interpretation indicating abnormal. This was crossed out and updated with a handwritten note indicating "normal" (**Attachment 1**). Additional information on the EKG record was crossed out and replaced with handwritten notes.

Firm's Response: Site management stated that the reviewing physician did not agree with the automatic interpretation.

OSIS Evaluation: After reviewing the EIR and exhibit (**Attachment 1**), this OSIS reviewer has some concerns about the electrocardiogram (EKG) for subject (b) (6) and would like to defer to DPARP for further evaluation. This reviewer agrees with investigator Deyampert's suggestion that the EKG could have been repeated if there were doubts about the original record and automatic interpretation.

Discussion Item 2:

Investigator Deyampert discussed the documentation of infusion volume for subjects (b) (6). The documentation stated that each of these subjects received 260 mL of study product. Subjects were supposed to have received 250 mL of study product (**Attachment 2**).

Firm's Response: Ms. Peppers, project manager, stated that the administered volume was recorded in error.

OSIS Evaluation: The EIR and exhibits had no records to confirm the infused volume or an error in recording. This reviewer recommends excluding study data from subjects (b) (6).

Discussion Item 3:

Based on the consent addendum for the planned follow-up visits, subjects (b) (6) with a positive antidrug antibodies result should return to the clinic to have a follow up blood sample and repeated testing. There were only two signed addenda on file for subjects (b) (6) who completed their visits.

Firm's Response: Ms. Peppers, project manager, stated that several attempts to contact the remaining subjects were unsuccessful.

OSIS Evaluation: This reviewer considers that there is no impact on the subjects' bioequivalence results. However, without the follow-up visits, there may have been a risk to subject safety. Ms. Deyampert discussed the importance of documenting activities that are pertinent to future studies.

Discussion Item 4:

The informed consents did not mention the information for clinicaltrials.gov (**Attachment 3**).

Firm's Response: There are no comments from the site.

OSIS Evaluation: This reviewer considers that there is no impact on subject safety or bioequivalence results, in that this portion of the study was conducted outside the United States.

Discussion Item 5:

The results reported by (b) (4) indicated that there was blood present in the urine for subject (b) (6). As such, the study team collected a second sample and performed testing with a local urine analyzer. The results were reported as negative.

Firm's Response: There are no comments from the site.

OSIS Evaluation: This reviewer considers that there is no impact on subject (b) (6) bioequivalence results and safety since the result was reported as negative. This reviewer agrees with Ms. Deyampert's recommendation to use the clinical pathology laboratory designated in the study protocol.

4. Conclusion:

After reviewing the inspectional findings, I conclude that data from study 20140108 (BLA 761086) are reliable, after excluding data from subjects (b) (6). In addition, the data from study of similar design that was not audited but submitted to pending applications (**Table 1**) are reliable for Agency review.

Based on the inspectional findings, studies of similar design conducted between the study start (November 2014) and end of the current surveillance interval should be considered reliable without an inspection.

Final Classification:

NAI - CMAX
(A division of Institute of Drug Technology (IDT), Australia Limited)
Adelaide, South Australia, Australia)
FEI#: 3013154634

cc:
OTS/OSIS/Kassim/Dasgupta/Mitchell/Fenty-Stewart/Taylor/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Au/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Kadavil/Choi/Skelly/Lewin/Li

ORA/OMPTO/OBIMO/FDAInternational_BIMO@fda.hhs.gov

Draft: XFL 10/08/2019; 10/9/2019; 10/10/2019
Edits: MFS 10/08/2019, 10/10/2019; XC 10/09/2019; JAK 10/11/2019

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/ CMAX (A division of Institute of Drug Technology (IDT), Australia Limited)
South Australia, Australia

[Redacted] (b) (4)

FACTS: 11920706

Table 1
Study not audited but submitted to pending application

Application #	Study #	Drug Name(s)	Dates of conduct
[Redacted] (b) (4)			

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MICHAEL F SKELLY
10/11/2019 03:47:30 PM

JOHN A KADAVIL
10/11/2019 03:50:48 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs/
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Erica Radden, M.D., Medical Officer
Division of Pediatric and Maternal Health (DPMH),
Office of Drug Evaluation IV (ODE IV),
Office of New Drugs (OND)

Through: John J. Alexander, M.D., M.P.H., Deputy Director
DPMH, ODE IV, OND

To: Division of Pulmonary, Allergy and Rheumatology
Products (DPARP)

Drug: Avsola (proposed biosimilar to U.S.-licensed Remicade
[infliximab])

Application Number: BLA 761086 (IND 122136)

Applicant: Amgen, Inc.

Proposed Indications: Treatment of:

- Crohn's Disease in adults
- Pediatric Crohn's Disease in patients 6 years and older
- Ulcerative Colitis in adults
- Pediatric Ulcerative Colitis in patients 6 years and older
- Rheumatoid Arthritis in adults
- Ankylosing Spondylitis in adults
- Psoriatic Arthritis in adults

- Plaque Psoriasis in adults

Proposed Dosage Form

& Route of Administration: Single-use vial containing 100 mg of lyophilized Avsola to be administered via intravenous infusion.

Proposed Dosing Regimen:

Crohn's Disease

5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response.

Pediatric Crohn's Disease

5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Ulcerative Colitis

5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Pediatric Ulcerative Colitis

5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Rheumatoid Arthritis

In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks.

Ankylosing Spondylitis

5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.

Psoriatic Arthritis and Plaque Psoriasis

5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Consult Request: DPARP requests the DPMH Pediatrics Team to assist with labeling for pediatric use.

Materials Reviewed:

- DPMH consult request (January 4, 2019 in DARRTS)
- Current U.S.-licensed Remicade (infliximab) labeling (September 19, 2018) per FDALabel
- Applicant's proposed labeling for Avsola (December 14, 2018)
- Prior DPMH review for Avsola/ABP 710 (IND 122136) dated January 26, 2018 in DARRTS
- Agreed upon initial Pediatric Study Plan (iPSP) for Avsola/ABP 710, IND 122136 (January 3, 2018 in DARRTS)
- Pediatric Review Committee Minutes for the December 20, 2017 meeting (dated January 17, 2018 in DARRTS)

- Pediatric Review Committee Minutes for the July 17, 2019 meeting (dated August 9, 2019 in DARRTS)

I. Consult and Regulatory Background:

On December 14, 2018, Amgen, Inc. submitted a BLA for Avsola under the 351(k) pathway as a proposed biosimilar to U.S.-licensed Remicade (infliximab) (hereinafter Remicade). Remicade is currently licensed by Janssen Biotech, Inc. and was first approved in 1998. Infliximab is a chimeric monoclonal antibody that neutralizes the biological activity of tumor necrosis factor alpha (TNF α) by binding with high affinity to the soluble and transmembrane forms of TNF α and inhibits binding of TNF α with its receptors.¹ TNF is a cytokine involved in inflammatory and immune responses, and elevated TNF levels also play a role in pathology of anti-inflammatory diseases.

Remicade has been previously approved for the following indications for which Amgen is seeking approval:

Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), Plaque Psoriasis (PsO), Crohn's Disease (CD), Pediatric CD, Ulcerative Colitis (UC), and Pediatric UC. (For additional regulatory background see DPMH's prior review for Avsola, IND 113461, dated May 24, 2016.) Remicade has no outstanding pediatric postmarketing requirements or commitments. Remicade was granted orphan designation for pediatric UC and pediatric CD, but the orphan exclusivity for these indications has expired. DPARP requested DPMH-Pediatrics team assistance in providing labeling recommendations for pediatric use.

II. Pediatric Study Plan:

Under PREA, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA. A pediatric assessment is required unless waived, deferred, or inapplicable. The Agency confirmed agreement with the agreed initial Pediatric Study Plan (iPSP) on January 3, 2018, which Amgen included in their BLA submission as their pediatric plan with no changes. Amgen proposed to demonstrate biosimilarity to Remicade and to provide an adequate justification under the BPCI Act to

¹ Current Remicade (infliximab) labeling (September 19, 2018)

support extrapolation of data and information to support licensure in certain non-studied indications; Amgen also proposed certain waivers. The agreed upon plan is summarized in Table 1. The rationale for the proposed waivers is summarized in Table 2.

Table 1. Overview of Pediatric Assessment Plan for Avsola

Indication	Age (years)	Plan for Pediatric Assessment
(b) (4)		

Source: Created by reviewer

Table 2. Proposed Full and Partial Waivers and Rationale

Indication	Age	Waiver Type	Criteria
(b) (4)			

Source: Amgen's agreed iPSP (January 3, 2018)

As explained in its pediatric study plan, (b) (4)

Remicade is approved only for, and Amgen is only seeking licensure for, treatment of adult patients with chronic severe (i.e., extensive and/or disabling) (b) (4)

Of note, the proposed 100 mg vial presentation, which is also approved for Remicade, provides an age-appropriate presentation for pediatric and adult patients for all proposed indications.

III. DPMH Review of labeling:

Consistent with Amgen's pediatric study plan, the Avsola labeling should incorporate relevant pediatric information from Remicade's labeling, including information regarding pediatric use in JIA patients 2 years and older and for pediatric UC and CD patients 6 years and older.²

This DPMH labeling review will focus on edits to the Highlights section and subsection 8.4 (Pediatric Use). Additions are proposed as underlined text and proposed deletions as strikethroughs in the relevant text.

Applicant's Proposed Labeling:

HIGHLIGHTS OF PRESCRIBING INFLIXIMAB INFORMATION

WARNING: SERIOUS INFECTIONS and MALIGNANCY

See full prescribing information for complete boxed warning.

- **Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as**

² See the July 2018 Labeling for Biosimilar Products Guidance for Industry.

histoplasmosis) and infections due to other opportunistic pathogens. (5.1)

- Discontinue TRADENAME if a patient develops a serious infection. (5.1)
- Perform test for latent TB; if positive, start treatment for TB prior to starting TRADENAME. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)
- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor (TNF) blockers, including infliximab products. (5.2)
- Postmarketing cases of fatal hepatosplenic T cell lymphoma (HSTCL) have been reported in patients treated with TNF blockers including infliximab products. Almost all had received azathioprine or 6 mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. The majority of cases were reported in patients with Crohn's disease or ulcerative colitis, most of whom were adolescent or young adult males. (5.2)

-----USE IN SPECIFIC POPULATIONS-----

Pediatric Use – TRADENAME Infliximab products ^{(b) (4)} have not been studied in children with Crohn's disease or ulcerative colitis <6 years of age. (8.4)

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS and MALIGNANCY

Patients treated with infliximab products are at increased risk for developing serious infections that may lead to hospitalization or death [*see Warnings and Precautions (5.1) and Adverse Reactions (6.1)*]. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

TRADENAME should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before TRADENAME use and during therapy.^{1,2} Treatment for latent infection should be initiated prior

to **TRADENAME** use.

- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

The risks and benefits of treatment with **TRADENAME should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.**

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with **TRADENAME, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.**

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF-blockers, including infliximab products [see *Warnings and Precautions (5.2)*].

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF-blockers including infliximab products. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males.

8 USE IN SPECIFIC POPULATIONS

8.4 PEDIATRIC USE

The safety and effectiveness of infliximab products have been established in pediatric patients 6 to 17 years of age for induction and maintenance treatment of Crohn's disease or ulcerative colitis. However, infliximab products have not been studied in children with Crohn's disease or ulcerative colitis <6 years of age.

Pediatric Crohn's Disease

TRADENAME is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy [see *Boxed Warning, Warnings and Precautions (5), Indications and Usage (1.2), Dosage and Administration (2.2), Clinical Studies (14.2) and Adverse Reactions (6.1)*].

Infliximab has been studied only in combination with conventional immunosuppressive therapy in pediatric Crohn's disease. The longer term (greater than 1 year) safety and effectiveness of infliximab products in pediatric Crohn's disease patients have not been established in clinical trials.

Pediatric Ulcerative Colitis

The safety and effectiveness of infliximab products for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients aged 6 years and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy are supported by evidence from adequate and well-controlled studies of infliximab (b) (4) in adults. Additional safety and pharmacokinetic data were collected in 60 pediatric patients aged 6 years and older [see *Clinical Pharmacology (12.3), Dosage and Administration (2.4), Adverse Reactions (6.1), and Clinical Studies (14.4)*]. The effectiveness of infliximab (b) (4) in inducing and maintaining mucosal healing could not be established. Although 41 patients had a Mayo endoscopy subscore of 0 or 1 at the Week 8 endoscopy, the induction phase was open-label and lacked a control group. Only 9 patients had an optional endoscopy at Week 54.

In the pediatric UC trial, approximately half of the patients were on concomitant immunomodulators (AZA, 6-MP, MTX) at study start. Due to the risk of HSTCL, a careful risk-benefit assessment should be made when TRADENAME is (b) (4) used in combination with other immunosuppressants.

The longer term (greater than 1 year) safety and effectiveness of infliximab products in pediatric ulcerative colitis patients have not been established in clinical trials.

Juvenile Rheumatoid Arthritis (JRA)

The safety and efficacy of infliximab in patients with juvenile rheumatoid arthritis (JRA) were evaluated in a multicenter, randomized, placebo-controlled, double-blind study for

14 weeks, followed by a double-blind, all-active treatment extension, for a maximum of 44 weeks. Patients with active JRA between the ages of 4 and 17 years who had been treated with MTX for at least 3 months were enrolled. Concurrent use of folic acid, oral corticosteroids (≤ 0.2 mg/kg/day of prednisone or equivalent), NSAIDs, and/or disease modifying antirheumatic drugs (DMARDs) was permitted.

Doses of 3 mg/kg infliximab or placebo were administered intravenously at Weeks 0, 2 and 6. Patients randomized to placebo crossed over to receive 6 mg/kg infliximab at Weeks 14, 16, and 20, and then every 8 weeks through Week 44. Patients who completed the study continued to receive open-label treatment with infliximab for up to 2 years in a companion extension study.

The study failed to establish the efficacy of infliximab in the treatment of JRA. Key observations in the study included a high placebo response rate and a higher rate of immunogenicity than what has been observed in adults. Additionally, a higher rate of clearance of infliximab was observed than had been observed in adults [*see Clinical Pharmacology (12.3)*].

A total of 60 patients with JRA were treated with doses of 3 mg/kg and 57 patients were treated with doses of 6 mg/kg. The proportion of patients with infusion reactions who received 3 mg/kg infliximab was 35% (21/60) over 52 weeks compared with 18% (10/57) in patients who received 6 mg/kg over 38 weeks. The most common infusion reactions reported were vomiting, fever, headache, and hypotension. In the 3 mg/kg infliximab group, 4 patients had a serious infusion reaction and 3 patients reported a possible anaphylactic reaction (2 of which were among the serious infusion reactions). In the 6 mg/kg infliximab group, 2 patients had a serious infusion reaction, 1 of whom had a possible anaphylactic reaction. Two of the 6 patients who experienced serious infusion reactions received infliximab by rapid infusion (duration of less than 2 hours). Antibodies to infliximab developed in 38% (20/53) of patients who received 3 mg/kg infliximab compared with 12% (6/49) of patients who received 6 mg/kg.

A total of 68% (41/60) of patients who received 3 mg/kg infliximab in combination with MTX experienced an infection over 52 weeks compared with 65% (37/57) of patients who received 6 mg/kg infliximab in combination with MTX over 38 weeks. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was pneumonia. Other notable infections included primary varicella infection in 1 patient and herpes zoster in 1 patient.

IV. Conclusion:

The PSP was reviewed by the Pediatric Review Committee on July 17, 2019. The PeRC concurred that no pediatric studies will be required but recommended [REDACTED] (b) (4)

[REDACTED] The pediatric assessment will be deemed complete if the applicant demonstrates biosimilarity and provides an adequate justification under the BPCI Act to support extrapolation of data and information to support licensure in the identified, non-studied indications. DPMH agrees with the outcome that no pediatric studies will be required under PREA for this application. Therefore, no pediatric postmarketing requirements will be issued.

DPMH reviewed the applicant's draft labeling and participated in the team meeting held on August 7, 2019. DPMH provided recommended labeling for the pediatric population based on labeling discussions between DPARP, the Office of Therapeutic Biologics and Biosimilars, and DPMH and in accordance with 21 CFR 201.57(c)(9)(iv). DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

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10/04/2019 12:44:07 PM

CLINICAL INSPECTION SUMMARY

Date	October 2, 2019
From	Min Lu, M.D., M.P.H., Medical Officer Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Katherine Clarridge, M.D., Medical Officer Stacy Chin, M.D., Clinical Team Leader Sally Seymour, M.D., Division Director Christine Ford, Regulatory Project Manager Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
BLA	761086
Applicant	Amgen
Drug	Avsola (ABP 710), proposed biosimilar to Remicade (infliximab)
NME	Yes
Therapeutic Classification	Tumor necrosis factor (TNF) blocker
Proposed Indication	Treatment of Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis
Consultation Request Date	February 12, 2019
Summary Goal Date	October 14, 2019
Action Goal Date	December 13, 2019
BsUFA Date	December 14, 2019

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Tomas Hala, and Olga Sleglova) were selected for inspection for a Phase 3 study (Protocol 20140111), entitled "A Randomized, Double-blind Phase 3 Study to Assess the Efficacy and Safety of ABP 710 Compared to Infliximab in Subjects with Moderate to Severe Rheumatoid Arthritis".

The study data derived from these two clinical sites, based on the inspections, are considered reliable and the study in support of this application appear to have been conducted adequately.

2. BACKGROUND

ABP710 is a monoclonal antibody (IgG1k) which binds tumor necrosis factor (TNF) that is currently being developed as a potential biosimilar for Remicade (infliximab).

Remicade (infliximab) is a TNF blocker initially approved in 1998 and it neutralizes the biological activity of TNF α by binding with high affinity to the soluble and transmembrane forms of TNF α and inhibits binding of TNF α with its receptors. The current approved indications of Remicade include the treatment of Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis in the United States (US).

In this application, the sponsor proposes ABP710 as a biosimilar product to the US-licensed Remicade reference product under section 351(k) of the Public Health Service Act (PHS Act). For this initial BLA, the Applicant intends to claim the same therapeutic indications for the proposed biosimilar ABP710 as those granted for Remicade in the US, with the exception of those indications protected by orphan drug exclusivity.

The ABP710 clinical development program included a pharmacokinetic (PK) study and a phase 3 study. The PK study (Study 20140108) was a 3-arm, single-dose PK and tolerability study in healthy subjects comparing ABP 710 to infliximab (US source) and infliximab (EU source). The Phase 3 study (Study 20140111) was a randomized, double-blind, active-controlled clinical study comparing efficacy, safety, PK, and immunogenicity of ABP 710 to infliximab (US source) in subjects with moderate to severe rheumatoid arthritis (RA), who have an inadequate response to methotrexate.

The review division requests inspection for the Phase 3 clinical trial (Study 20140111). The PK study in healthy subjects is inspected by the Office of Study Integrity and Surveillance.

Protocol 20140111

Protocol Title: A Randomized, Double-blind Phase 3 Study to Assess the Efficacy and Safety of ABP 710 Compared to Infliximab in Subjects With Moderate to Severe Rheumatoid Arthritis

This was phase 3, randomized, double-blind, active-controlled, multiple-dose, clinical similarity study was designed to evaluate the efficacy, safety, and immunogenicity of ABP 710 compared with infliximab (US source) in adult subjects with moderate to severe rheumatoid arthritis (RA) who have an inadequate response to methotrexate (MTX).

The primary objective of this study was to assess the efficacy of ABP 710 compared with infliximab. The secondary objectives were to assess the safety and immunogenicity of ABP 710 compared with infliximab.

The primary efficacy endpoint was the ACR 20 (20% improvement as defined by American College of Rheumatology) response rate at Week 22.

The study main inclusion criteria included subjects aged 18 to 80 years with a diagnosis of RA (duration of at least 3 months). Subjects were to have active RA, defined as ≥ 6 swollen joints and ≥ 6 tender joints (based on 66/68 joint count excluding distal interphalangeal joints) at screening and baseline, and at least 1 of the following at screening: erythrocyte sedimentation rate ≥ 28 mm/hour or serum C-reactive protein (CRP) > 1.0 mg/dL. Subjects were also to have a positive rheumatoid factor and/or anti-cyclic citrullinated peptide at screening and were to have taken MTX for ≥ 12 consecutive weeks and be on a stable dose of oral or subcutaneous MTX 7.5 to 25 mg/week for ≥ 8 weeks before receiving investigational product. Subjects were excluded from participation if they had class IV RA according to the American College of Rheumatology (ACR) revised response criteria, if they had Felty's syndrome (RA, splenomegaly, and granulocytopenia), or if they had a history of prosthetic or native joint infection. Subjects were also excluded if they had previously received infliximab or an infliximab biosimilar. Subjects who had previously received other commercially available or investigational biologic therapies for RA (including other anti-tumor necrosis factor alpha inhibitors) were allowed to participate in the study provided a predetermined amount of time had elapsed before the first dose of investigational product.

Subjects were initially randomized in a 1:1 ratio to receive a 3mg/kg intravenous (IV) infusion of either ABP 710 or infliximab on day 1 (Week 0), at Weeks 2 and 6, and every 8 weeks thereafter until Week 22. At Week 22, subjects initially randomized to infliximab were re-randomized in a 1:1 ratio to either continue receiving infliximab every 8 weeks or transition to receive ABP 710 every 8 weeks through Week 46. Subjects initially randomized to ABP 710 continued receiving the same treatment every 8 weeks through Week 46.

The study randomized 558 subjects from 75 centers in Australia, Bulgaria, Canada, Czech Republic, Germany, Hungary, Poland, Spain, and the United States (U.S.).

The study enrolled the first subject on October 10, 2016. The data cutoff date for primary analysis for the study report was April 16, 2018.

Rationale for Site Selection

The two clinical sites were selected using a clinical investigator site selection tool based on their high enrollment and high discontinuation rates. Site 11121004 (Dr. Tomas Hala's site) had five discontinuations and all of them were in the ABP710 arm of the study. Site 11121001 (Dr. Olga Sleglova's site) had seven discontinuations. Both sites had comparatively high enrollment numbers.

3. RESULTS (by site):

1) Tomas Hala, M.D. (CCR, Inc., Trida Miru 2800 Pardubice 2, 530 02, Czech Republic; Inspection dates: May 20-28, 2019)

This site screened 52 subjects and enrolled 31 subjects for Study 20140111. Among the 31 enrolled subjects, 26 subjects completed the study treatment and five subjects (all in the ABP710 group) discontinued treatment prematurely. The reasons for discontinuations included adverse events (Subject (b) (6): after Week 6 due to endometrial adenocarcinoma; Subject (b) (6): after Week 38 due to malignant melanoma located right paravertebrally), consent withdrawal due to lack of efficacy (Subjects (b) (6)), and other unspecified (Subject (b) (6)). An audit was conducted for 29 of 31 enrolled subjects.

The inspection evaluated the following documents: informed consent, screening and enrollment logs, eligibility criteria, medical records, case report forms, study drug accountability logs, study monitoring visits, primary and secondary efficacy endpoints, adverse event reporting, laboratory reports, Independent Ethics Committee (IEC) oversight, and financial disclosures. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable. No under-reporting of adverse events was noted. Discontinuations were verifiable.

At the conclusion of the inspection, the following item was discussed with the clinical investigator at the close-out meeting:

Subject (b) (6) (randomized in the infliximab control group) should have been excluded due to having received an intra-articular steroid injection 25 days prior to randomization when the washout period required 28 days per protocol.

Although this protocol violation was noted, it is unlikely to have significant impact on the primary efficacy endpoint of the study. In general, this clinical site appeared to be in compliance with Good Clinical Practices except item described as above. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site is acceptable in support of this application.

2) Olga Sleglova, M.D. (Revmatologický ústav, Na Slupi 4, 12850 Praha 2, Czech Republic; Inspection dates: May 9-17, 2019)

This site screened 25 subjects and enrolled 22 subjects for Study 20140111. Among the 22 enrolled subjects, 26 subjects completed the study treatment and seven subjects discontinued treatment prematurely. The reasons for discontinuations included worsening of RA (Subject

(b) (6) in the ABP710 group and Subject (b) (6) in the infliximab group), hypersensitivity reactions (Subject (b) (6) in the ABP710 group and Subject (b) (6) in the infliximab group), other adverse events (Subject (b) (6) in the ABP710 group experienced influenza and Subject (b) (6) in the infliximab group had left hip replacement surgery for osteoarthritis), and consent withdrawal (Subject (b) (6) in the infliximab group). An audit was conducted for all 22 enrolled subjects.

The inspection evaluated the following documents: informed consent, protocol adherence, inclusion/exclusion criteria, adverse event reporting, Independent Ethics Committee (IEC) oversight, primary and secondary efficacy endpoints, adverse event reporting, concomitant medications, investigational product exposure, and discontinuations. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and subject line listings. There were no limitations during conduct of the clinical site inspection.

The primary and secondary efficacy endpoints were verifiable. Discontinuations and major protocol deviations were reported. No under-reporting of serious adverse events was noted.

At the conclusion of the inspection, the following items were discussed with the clinical investigator at the close-out meeting:

1. There was no contemporaneous documentation for the destruction of six kits of ABP 710 and three kits of infliximab in the accountability records.
2. There was one un-reported concomitant medication (Chondroitin Sulfate 11/21/17-2/27-18) for Subject (b) (6) (in the ABP710 group).

Although the above violations were noted, they appear unlikely to have significant impact on the primary efficacy endpoint of the study. In general, this clinical site appeared to be in compliance with Good Clinical Practices except the item described as above. Data submitted by this clinical site appear acceptable in support of this specific indication.

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch

Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm.

Review Division / Acting Clinical Team Leader/ Stacy Chin

Review Division/Medical Officer/ Katherine Clarridge

Review Division /Project Manager/ Christine Ford

OSI/DCCE/ Division Director/Ni Khin

OSI/DCCE/Branch Chief/Kassa Ayalew

OSI/DCCE/GCP Reviewer/Min Lu

OSI/ GCP Program Analyst/Yolanda Patague

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MIN LU
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
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: August 28, 2019

Requesting Office or Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Application Type and Number: BLA 761086

Product Name, Dosage Form, and Strength: Avsola^a
(infliximab-axxq)
For Injection
100 mg/vial

Product Type: Single Ingredient Product

Rx or OTC: Rx

Applicant/Sponsor Name: Amgen, Inc.

FDA Received Date: December 14, 2018 and June 21, 2019

OSE RCM #: 2018-2747

DMEPA Safety Evaluator: Teresa McMillan, PharmD

DMEPA Team Leader: Idalia E. Rychlik, PharmD

^a The proposed proprietary name Avsola and the nonproprietary name infliximab-axxq were found conditionally acceptable for BLA 761086 on February 21, 2019 and March 1, 2019 respectively.

1 PURPOSE OF REVIEW

As part of the approval process for Avsola (infliximab-axxq) for Injection, 100 mg/vial, we reviewed the proposed Prescribing Information (PI), carton labeling, container label for areas 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 for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted PI, label and labeling, DMEPA’s rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Prescribing Information			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Issues			
1.	The proposed proprietary name Avsola and nonproprietary name infliximab-axxq were found conditionally acceptable.	The proprietary name and the nonproprietary name are needed for identification of the drug product.	Revise the proprietary name throughout labeling to read ‘Avsola’ and the nonproprietary name to read infliximab-axxq.

2.	In Section 16, How Supplied/Storage and Handling, the NDC number has been omitted.	The NDC number is needed for identification of the drug product.	List the NDC number in Section 16, How Supplied/Storage and Handling.
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Table 3: Identified Issues and Recommendations for Amgen (entire table to be conveyed to Applicant)

Container Labels and Carton Labeling			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	Your proposed proprietary name Avsola was found conditionally acceptable.	The proprietary name is needed for identification of the drug product.	Revise the proprietary name throughout the labels and labeling to read 'Avsola'.
2.	The expiration date format is not defined.	Lack of a defined expiration date may lead to deteriorated drug product errors and is needed in order that we assess it from a medication error perspective.	As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the 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.
Carton Labeling			
1.	The “Discard unused portion” statement has been omitted from the Single Dose statement.	Inclusion of this statement helps minimize the risk of the entire contents of the vial being given as a single dose.	Consider revising the Single Dose statement to the following on the principal display panel: Single-Dose Vial. Discard unused portion.
2.	The Usual Dose statement is not clearly defined.	Inclusion of the Usual Dose helps minimize dosing and administration errors.	Consider revising the Usual Dose statement to the following and relocate “Reconstitute each vial with 10 mL Sterile Water for Injection, USP” under the Usual Dose statement: For example: Recommended Dosage: See prescribing information. Reconstitute each vial with 10 mL Sterile Water for Injection, USP. Do NOT shake reconstituted solution. Must further dilute with 0.9% Sodium Chloride Injection, USP. Once reconstituted, each mL contains 10 mg infliximab-axxq, dibasic sodium phosphate, anhydrous (0.49 mg), monobasic sodium phosphate, monohydrate (0.22 mg), polysorbate 80 (0.05 mg), and sucrose (50 mg).” The alphabetical order of the inactive ingredients is

			consistent with the prescribing information.
3.	The “Dispense the enclosed Medication Guide to each patient” statement has been omitted.	Inclusion of this statement is required per 21 CFR 208.24(d) and 21 CFR 610.60(a)(7) .	Per 21 CFR 208.24(d) and 21 CFR 610.60(a)(7) include the following statement of the principal display panel: “ATTENTION: Dispense the enclosed Medication Guide to each patient”
4.	In the “How Supplied” section of the Prescribing Information, there is an accumulator carton containing 10 vial containers, but the proposed labeling for the accumulator carton wasn’t submitted for evaluation.	This product labeling should be submitted to the Agency for review.	Submit your proposed labeling for the accumulator carton containing 10 vials for Agency review.
5.	The storage information is incomplete.	Lack of complete storage information could lead to deteriorated drug product errors.	Revise the storage information to the following and relocate to a side or back panel: Store unopened vial in refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to Protect from Light. Unopened vials may also be stored at temperatures up to a maximum of 30°C (86°F) for a single period of up to 6 months. If stored under these conditions discard after ___/___/___. See Prescribing Information.
6.	Important reconstitution and dilution information has been omitted.	Lack of this information may lead to administration errors.	Add the following to the principal display panel: Reconstitute and Dilute before Intravenous Infusion. Infuse over at least 2 hours with an in-line filter.

7.	The net quantity statement is in close proximity to the product strength.	Numerical confusion between the strength and the net quantity statement may occur.	Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.
8.	As currently presently, the route of administration statement lacks prominence on the principal display panel.	Lack of prominence of the route of administration may contribute to wrong route of administration errors.	Relocate the route of administration statement to appear on the principal display panel underneath the strength statement as follows: Proprietary name Proper name For injection 100 mg/vial For Intravenous Infusion Only If space is limited, consider removing or decreasing the prominence of the blue/green graphic to allow room for this important information.
Container Label			
1.	The Usual Dose statement has been omitted.	Inclusion of the Usual Dose helps to minimize dosing and administration errors.	Consider adding the following: Recommended Dosage: See Prescribing Information
2.	The “Single-Dose Vial. Discard unused portion” statement has been omitted.	Inclusion of this statement helps minimize the risk of the entire contents of the vial being given as a single dose.	Refer to the Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable

			<p><u>Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, October 2018</u></p> <p>Consider including the following: Single-Dose Vial. Discard unused portion.</p>
3.	The dosage form has been omitted.	Inclusion of the dosage form helps to minimize administration errors.	<p>Consider including the following:</p> <p>Proprietary name Proper name For injection 100 mg/vial For Intravenous Infusion Only</p> <p>If space is limited, consider using only 2 lines instead of 3 lines of text for the manufacturer information and the U.S. license.</p>

4 CONCLUSION

Our evaluation of the proposed labels and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in **Table 2** for the **Division** and **Table 3** for **Amgen**. We ask that the Division convey Table 3 in its entirety to Amgen so that recommendations are implemented prior to approval of this BLA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Avsola that Amgen, Inc. submitted on June 21, 2019, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and Avsola		
Product Name	Remicade	Avsola
Initial Approval Date	08/24/1998	N/A
Proper or nonproprietary name	Infliximab	infliximab-axxq
Indication	Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Pediatric Ulcerative Colitis, Rheumatoid Arthritis Ankylosing Spondylitis, Psoriatic Arthritis and Plaque Psoriasis.	Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Pediatric Ulcerative Colitis, Rheumatoid Arthritis Ankylosing Spondylitis, Psoriatic Arthritis and Plaque Psoriasis.
Route of Administration	Intravenous	Intravenous
Dosage Form	Lyophilized powder for injection	Lyophilized powder for injection
Strength	100 mg/vial	100 mg/vial
Dose and Frequency	<p>Administered by intravenous infusion over a period of not less than 2 hours.</p> <p><i>Crohn's Disease:</i> 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response.</p> <p><i>Pediatric Crohn's Disease:</i> 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.</p> <p><i>Ulcerative Colitis:</i> 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.</p>	<p>Administered by intravenous infusion over a period of not less than 2 hours.</p> <p><i>Crohn's Disease:</i> 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response.</p> <p><i>Pediatric Crohn's Disease:</i> 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.</p> <p><i>Ulcerative Colitis:</i> 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.</p>

	<p><i>Pediatric Ulcerative Colitis:</i> 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.</p> <p><i>Rheumatoid Arthritis:</i> In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks.</p> <p><i>Ankylosing Spondylitis:</i> 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.</p> <p><i>Psoriatic Arthritis and Plaque Psoriasis:</i> 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.</p>	<p><i>Pediatric Ulcerative Colitis:</i> 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.</p> <p><i>Rheumatoid Arthritis:</i> In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks.</p> <p><i>Ankylosing Spondylitis:</i> 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.</p> <p><i>Psoriatic Arthritis and Plaque Psoriasis:</i> 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.</p>
How Supplied	20 mL vial is individually packaged in a carton. Supplied in an accumulator carton containing 10 vials	20 mL vial is individually packaged in a carton. Supplied in an accumulator carton containing 10 vials, as well as in a single carton containing 1 vial. ^b
Storage	Refrigerated at 2°C to 8°C (36°F to 46°F). Do not use beyond the expiration date located on the carton and the vial. This product contains no preservative. Unopened vials may also be stored at temperatures up to a maximum of 30°C (86°F) for a single period of up to 6 months but not exceeding the original	Refrigerated at 2°C to 8°C (36°F to 46°F). Do not use beyond the expiration date located on the carton and the vial. This product contains no preservative. Unopened vials may also be stored at temperatures up to a maximum of 30°C (86°F) for a single period of up to 6 months but not exceeding the original

^b As noted above, the Applicant has not submitted the proposed labeling for the accumulator carton, and we recommend requesting that the Applicant submit the proposed labeling for Agency review.

	expiration date. The new expiration date must be written on the carton. Upon removal from refrigerated storage, cannot be returned to refrigerated storage.	expiration date. The new expiration date must be written on the carton. Upon removal from refrigerated storage, cannot be returned to refrigerated storage.
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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,^c along with postmarket medication error data, we reviewed the following Avsola labels and labeling submitted by Amgen Inc. on June 21, 2019.

- Container label received on June 21, 2019
- Carton labeling received on June 21, 2019
- Prescribing Information (Image not shown) received on June 21, 2019

F.2 Label and Labeling Images

Container Label



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

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/s/

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Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 8-20-2019 **Date Consulted:** 1-4-2019

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara N. Johnson, M.D., M.S.
Team Leader, Maternal Health
Division of Pediatric and Maternal Health

To: Division of Pulmonary, Allergy, and Rheumatology Products

Drug: Avsola¹ (proposed biosimilar to Remicade (infliximab)); intravenous injection;
BLA 761086

Applicant: Amgen

Proposed Indications: Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Labeling as part of 351(k) biosimilar application

Materials Reviewed:

- Applicant's proposed labeling and review of the literature
- Remicade (reference product) approved labeling (6-19-2018)
- Ixifi labeling (biosimilar to Remicade, approved labeling (12-13-2017))
- Literature review
- DPMH Remicade review of Nordic Pregnancy Register final report and PIANO Pregnancy Registry data (6-2-2017)

¹ Proposed proprietary name.

- DPMH Ixifi PLLR review (11-30-2017)

Consult Question: Please review the Pregnancy and Lactation Labeling Rule (PLLR) Labeling

INTRODUCTION

The applicant submitted a 351(k) BLA for Avsola, a proposed biosimilar to Remicade (infliximab) on 12-14-2018. The proposed indications are the following (the same as the reference product):

- Crohn's Disease :
 - reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
 - reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease.
- Pediatric Crohn's Disease :
 - reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Ulcerative Colitis :
 - reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Pediatric Ulcerative Colitis :
 - reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Rheumatoid Arthritis in combination with methotrexate :
 - reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active disease.
- Ankylosing Spondylitis :
 - reducing signs and symptoms in patients with active disease.
- Psoriatic Arthritis :
 - reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.
- Plaque Psoriasis :
 - treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) consulted the Division of Pediatric and Maternal Health (DPMH) on 1-4-2019, to assist with reviewing the Pregnancy and Lactation subsections of labeling.

BACKGROUND

Product Background

Drug Class and Description	Chimeric IgG1 κ monoclonal antibody specific for human tumor necrosis factor (TNF) α
Remicade Approval Date	1998
Mechanism of Action	<ul style="list-style-type: none"> Neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors TNF is a cytokine involved in inflammatory and immune responses, and elevated TNF levels play a role in pathology of inflammatory diseases
Molecular Weight	149,100 Daltons
Half-life	7.7 to 9.5 days
Dosing Regimen	Induction at 0, 2, and 6 weeks, then maintenance every 8 weeks
Serious Adverse Reactions	Serious infections, malignancy
Other Approved Biosimilars	Inflectra, (4-4-2016), Renflexis (4-21-2017), Ixifi (12-13-2017)

Current state of the labeling of Remicade (6-19-2018)

Format	Physician Labeling Rule (PLR)
Warnings and Precautions (W & P) 5.15 Live Vaccines/Therapeutic Infectious Agents	<ul style="list-style-type: none"> A statement that infliximab has been detected in the serum of infants up to 6 months after birth, and that these infants may be at increased risk of fatal infection. There is a recommendation to not administer live vaccines to infants until after 6 months of age. Cases of agranulocytosis in infants exposed <i>in utero</i> have been reported
8.1 Pregnancy	<ul style="list-style-type: none"> Category B It is not known whether Remicade can cause fetal harm No human data Animal reproduction studies that showed no adverse developmental effects at doses up to 40 mg/kg The same statement that is included in W & P
Nursing Mothers	<ul style="list-style-type: none"> It is not known whether Remicade is excreted in human milk or absorbed systemically after ingestion

	<ul style="list-style-type: none"> • Because of the potential for adverse reactions in nursing infants, women should not breastfeed • Discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother.
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Current state of the labeling of Ixifi²

Currently approved Ixifi labeling (12-13-2017) includes the following information:

8.1 Pregnancy

- Risk Summary
 - A statement that available data from published literature on the use of infliximab products during pregnancy have not reported a clear association with infliximab products and adverse pregnancy outcomes
 - A statement that infliximab products cross the placenta
 - A recommendation that infants exposed *in utero* should not be administered live vaccines for at least 6 months after birth
 - Animal reproduction studies that showed no adverse developmental effects
- Clinical Considerations
 - Fetal/neonatal adverse reactions
 - A statement that infliximab products have been detected in the serum of infants up to 6 months following birth
 - A statement on the potential increased risk of infection in infants who were exposed *in utero*
 - A recommendation to avoid administering live vaccines to *in utero* exposed infants in the first six months of life
 - Cases of agranulocytosis in infants exposed *in utero* have been reported
- Data
 - Animal data that support the information in the risk summary

8.2 Lactation

- Risk Summary
 - A statement that available information is insufficient to inform the amount of infliximab products in human milk and the effect on the breastfed infant, and that there are no data on the effects of infliximab products on milk production.

REVIEW OF DATA

Pregnancy

Nonclinical Experience

² Ixifi labeling presented here is informational only, as it is the most recently approved infliximab biosimilar to Remicade.

Because infliximab does not cross-react with TNF α in species other than humans and chimpanzees, animal reproduction studies have not been conducted with infliximab products Avsola or Remicade. No adverse developmental effects were seen in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNF α at doses up to 40 mg/kg. No additional reproductive and developmental nonclinical studies were conducted for this 351(k) BLA. Please refer to the Nonclinical PLLR review by Drs. Steve Leshin and Carol Galvis.

Review of Human Pregnancy Data

Applicant's literature review

The applicant provided a review of a published European prospective cohort study of 168 exposures to infliximab products in pregnancy that showed no pattern of malformations.³ The applicant's conclusion that the literature shows no increased risk of malformations is consistent with the literature that DPMH had previously reviewed for the Ixifi application.⁴

DPMH Literature Review

DPMH performed a search of published literature on infliximab products and pregnancy and did not identify any new publications that affect the risk conclusion, since the last DPMH review of 3-31-2017. This reviewer identified two new published studies with small sample sizes of pregnant women exposed to infliximab products (n=11⁵ and n=78⁶) that showed no increased risk of major malformations.

Review of Pharmacovigilance Database

The applicant's safety database included no pregnancy cases reports following exposure to infliximab products.

Applicant's Conclusion

The applicant concluded that there is no new or significant safety information that warrants inclusion in labeling.

Previous DPMH Review of post-marketing data submitted by Remicade manufacturer, Janssen

In a review dated 6-2-2017, DPMH reviewed the final report from the Nordic Register, which is a post-marketing commitment (PMC), and data from the US based PIANO (Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes) Pregnancy Registry. DPARP is currently reviewing these final study reports in collaboration with DPMH, the Division of Epidemiology II in the Office of Surveillance and Epidemiology, and the Division of Biostatistics VII.

³ Weber-Schoendorfer C, Oppermann M, Wacker E, et al. Pregnancy outcome after TNF- α inhibitor therapy during the first trimester: a prospective multicentre cohort study. *Br J Clin Pharmacol* 2015; 80:727–39.

⁴ See review in DARRTS dated 11-30-2017, Reference ID 4187171

⁵ Genest G., Spitzer K. and Laskin C. "Maternal and fetal outcomes in a cohort of patients exposed to tumor necrosis factor inhibitors throughout pregnancy." *Arthritis and Rheumatology* (2017) 69 (Supplement 10).

⁶ Lichtenstein G. R., Feagan B. G., Mahadevan U., Salzberg B. A., Langholff W., Morgan G. J., et al. "Pregnancy Outcomes Reported During the 13-Year TREAT Registry: A Descriptive Report." *American Journal of Gastroenterology* (2018).

Summary

Available data from published literature on the use of infliximab products during pregnancy have not reported a clear association with infliximab products and adverse pregnancy outcomes. Therefore, it is appropriate to include a risk summary statement in labeling that reflects this conclusion.

Lactation

Nonclinical Experience

Currently approved Remicade labeling does not include any nonclinical data. No additional nonclinical studies were submitted with this 351(k) BLA.

Review of Human Lactation Data

Applicant's Literature Review

The applicant stated that there is no available lactation information on infliximab products.

Review of Pharmacovigilance Database

The applicant performed a review of their pharmacovigilance safety database for cases of infliximab product use and lactation, and did not identify any cases.

Applicant's Conclusion

The applicant concludes that there is no information for inclusion in labeling.

DPMH Literature Review

DPMH conducted a search of *Medications and Mother's Milk*⁷, the Drugs and Lactation Database (LactMed),⁸ and of published literature in PubMed and Embase using the search terms "infliximab and lactation" and "infliximab and breastfeeding." This reviewer identified a new published lactation study.⁹ In an e-mail dated 8-19-2019, Dr. Stacy Chin communicated that DPARP has determined that the Clinical Pharmacology review of this published study will be addressed as part of the PLLR labeling conversion of Remicade. Therefore, addition of lactation data to Avsola labeling is deferred, pending review of these data.

Summary

Available information is insufficient to inform the amount of infliximab products present in human milk and the effect on breastfed infants, and there are no data on the effects of infliximab products on milk production. Therefore, it is appropriate to include risk summary statements in

⁷ Hale, Thomas (2019) Medications and Mothers' Milk online

⁸ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation when available on drug levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

⁹ Matro R, Martin CF, Wolf D, Shah SA, Mahadevan U. Gastroenterology. 2018 Sep;155(3):696-704. Exposure Concentrations of Infants Breastfed by Women Receiving Biologic Therapies for Inflammatory Bowel Diseases and Effects of Breastfeeding on Infections and Development.

labeling that reflect these conclusions. There is a new published lactation study since the previous DPMH review dated 11-30-2017. DPARP has determined that Clinical Pharmacology review of this study will be addressed as part of the PLLR labeling conversion of Remicade. Therefore, addition of lactation data to Avsola labeling is deferred, pending review of these data.

Females and Males of Reproductive Potential

Nonclinical Experience

Currently approved Remicade labeling includes nonclinical data that showed no effects on fertility. No additional nonclinical studies were submitted with this 351(k) BLA.

Review of Data

Applicant's Literature Review

The applicant did not include a literature review of infertility effects following exposure to infliximab products.

DPMH Literature Review

DPMH performed a search of published literature on infliximab products and infertility and did not identify any new publications.

Review of Pharmacovigilance Database

The applicant did not state whether there are any infertility cases in their pharmacovigilance safety database.

Summary

There are no new data on infliximab products and infertility since the last DPMH review of 1-30-2017. Animal reproductive studies of administration of infliximab did not show any adverse effects on fertility. Additionally, since available human data do not suggest an effect of infliximab products on fertility, Subsection 8.3, Females and Males of Reproductive Potential, will not be included in Avsola labeling.

DISCUSSION

Pregnancy

There are no new data that affect the risk conclusion on the safety of infliximab products in pregnancy since the previous Ixifi DPMH review dated 11-30-2017. Therefore, the labeling for Avsola will include the same information as the labeling for Ixifi. The final study report from the Remicade Nordic Pregnancy Register and a study report from the PIANO Pregnancy Registry are currently being reviewed by the Agency. These studies have larger sample sizes than currently available studies, and may help assess the overall risk profile of exposure to infliximab products in pregnancy. Addition of human data to labeling is deferred, pending review of these data.

Lactation

There are no new data that affect the risk conclusion on the safety of infliximab products in lactation, since the previous Ixifi DPMH review dated 11-30-2017. Therefore, the labeling for Avsola will include the same information as the labeling for Ixifi. There is a new published lactation study since the previous DPMH review dated 11-30-2017. DPARP has determined that

Clinical Pharmacology review of this study will be addressed as part of the PLLR labeling conversion of Remicade. Therefore, addition of lactation data to Avsola labeling is deferred, pending review of these data.

CONCLUSION

The Pregnancy and Lactation subsections of the proposed Avsola labeling were structured to be consistent with the PLLR. DPMH has the following recommendations for the Avsola labeling:

- **8.1 Pregnancy**
 - The “Pregnancy” subsection of Avsola labeling was formatted in the PLLR format to include “Risk Summary”, “Clinical Considerations, Fetal/neonatal adverse reactions”, and “Data” sections
- **8.2 Lactation**
 - The “Lactation” subsection of Avsola labeling was formatted in the PLLR format to include the “Risk Summary” and “Data” sections.

DPMH LABELING RECOMMENDATIONS¹⁰

DPMH recommendations are below. **See final labeling for all of the labeling revisions negotiated with the applicant.**

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published literature on the use of infliximab products during pregnancy have not reported a clear association with infliximab products and adverse pregnancy outcomes. Infliximab products cross the placenta and infants exposed in utero should not be administered live vaccines for at least 6 months after birth (*see Clinical Considerations*). No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental study conducted in mice using an analogous antibody (b) (4) (see *Data*).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/neonatal adverse reactions

Infliximab products cross the placenta, and have been detected in the serum of infants up to 6 months following birth. Consequently, these infants may be at increased risk of infection,

¹⁰ We are separately evaluating the inclusion of certain information derived from literature in the labeling for applications approved under section 351(a) of the PHS Act. The inclusion of certain information in the Avsola labeling that is derived from literature does not affect our evaluation of that issue.

including disseminated infection which can become fatal. At least a six month waiting period following birth is recommended before the administration of live vaccines (e.g., BCG vaccine or other live vaccines, such as the rotavirus vaccine) to these infants [see *Warnings and Precautions* (5.14)]. Cases of agranulocytosis in infants exposed in utero have also been reported [see *Adverse Reactions* (6.2)].

Data

Animal Data

Because infliximab products do not cross-react with TNF α in species other than humans and chimpanzees, animal reproduction studies have not been conducted with infliximab products. No evidence of maternal toxicity ^(b)₍₄₎ embryotoxicity ^(b)₍₄₎ functional activity of mouse TNF α . Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. ^(b)₍₄₎

8.2 Lactation

Risk Summary

Available information is insufficient to inform the amount of infliximab products present in human milk, and the effect on breastfed infants. There are no data on the effects of infliximab products on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for an infliximab product and any potential adverse effects on the breastfed infant from infliximab products or from the underlying maternal condition.

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/s/

LEYLA SAHIN
08/20/2019 10:38:04 AM

TAMARA N JOHNSON
08/21/2019 08:40:23 AM

MEMORANDUM

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

DATE: 4/12/2019

TO: Division of Pulmonary, Allergy and Rheumatology Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

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

RE: BLA 761086

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

Nucleus Network, Melbourne: The Office of Regulatory Affairs (ORA) inspected the site in December 2017, which falls within the surveillance interval. The inspection was conducted under the following submission: BLA 761073.

The final classification for the inspection was No Action Indicated (NAI).

(b) (4) OSIS inspected the site in March 2019 under the following submissions: NDAs (b) (4). No Form FDA 483 was issued at the close of the inspection. The Establishment Inspection Report review is still pending.

However, prior to March 2019, OSIS inspected the site in (b) (4) under the following submissions: BLAs (b) (4). The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the outcome of the previous inspections and the rationale described above, an inspection is not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Nucleus Network, Ltd.	The Centre for Clinical Studies, 5 th Floor, Burnet Tower, AMREP Precinct, 89 Commercial Road, Melbourne, Victoria, Australia
Analytical		(b) (4)

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/s/

NICOLA M FENTY-STEWART
04/12/2019 10:03:29 AM