CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761054Orig1s000

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

This memorandum supersedes and replaces the DMPP Patient Labeling Review memorandum dated April 10, 2017, which was prematurely finalized while still under review.

Date:	April 20, 2017
To:	Badrul Chowdhury, MD, PhD 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)**
	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (nonproprietary name):	RENFLEXIS (infliximab-abda[1])
Dosage Form and Route:	Injection, for Intravenous Use
Application Type/Number:	BLA 761054
Applicant:	Samsung Bioepis Co., Ltd.

[1] At the time of the original submission, a four letter suffix for the nonproprietary name for RENFLEXIS had not been determined. Subsequent to submission of the 351(k) BLA, the nonproprietary name for RENFLEXIS was determined to be infliximab-abda.

1 INTRODUCTION

This memorandum supersedes and replaces the DMPP Patient Labeling Review memorandum dated April 10, 2017, which was prematurely finalized while still under review.

On March 21, 2016, Samsung Bioepis Co., Ltd. submitted for the Agency's review a 351(k) Biologics License Application (BLA) for RENFLEXIS (infliximab-abda) for Injection, for Intravenous Use. The Applicant seeks approval for RENFLEXIS (infliximab-abda) 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.

On January 5, 2017, the Applicant submitted a major amendment to their pending application; therefore, the Agency extended the user fee goal date to April 21, 2017

The Applicant has proposed RENFLEXIS (infliximab-abda) for Injection, for Intravenous Use, for the following indications[2]:

Crohn's Disease:

- for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.
- for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.

Pediatric Crohn's Disease:

- for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Chrohn's disease who have had an inadequate response to conventional therapy.

Ulcerative Colitis:

- for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

Rheumatoid Arthritis:

[2] We note that REMICADE's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. Accordingly, FDA will not be able to license a proposed biosimilar product for this indication until the orphan exclusivity expires.

- in combination with methotrexate, for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely rheumatoid arthritis.

Ankylosing Spondylitis:

- for reducing signs and symptoms in patients with active ankylosing spondylitis.

Psoriatic Arthritis:

- for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.

Plaque Psoriasis

- for the 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.

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 July 28, 2016 for DMPP to review the Applicant's proposed Medication Guide (MG) for RENFLEXIS (infliximab-abda) for Injection, for Intravenous Use.

2 MATERIAL REVIEWED

- Draft RENFLEXIS (infliximab-abda) for Injection, for Intravenous Use MG received on March 21, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on February 23, 2017.
- Draft RENFLEXIS (infliximab-abda) for Injection, for Intravenous Use Prescribing Information (PI) received on March 21, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on February 23, 2017.
- Approved REMICADE (infliximab) Lyophilized Concentrate for Injection, for Intravenous Use labeling dated October 2, 2015.
- Approved INFLECTRA (infliximab-dyyb) for Injection, for Intravenous Use labeling dated April 5, 2016.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our review of the MG we have:

- ensured that the MG is consistent with the Prescribing Information (PI)
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the presentation of information in the MG is consistent with the format of the approved MG for the reference product 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.

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/s/

SHARON R MILLS
04/20/2017

LASHAWN M GRIFFITHS
04/20/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
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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 New Drugs (OND)
Through:	John J. Alexander, M.D., M.P.H., Deputy Director DPMH, OND
To:	Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Drug:	SB2 (proposed biosimilar to Remicade [infliximab])
Application Number:	BLA 761054
Re:	Review of Pediatric Use Labeling
Sponsor:	Samsung Bioepis Co., Ltd.
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 [1]

[1] This reflects information for SB2 that Samsung submitted on March 31, 2016. We note that the indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23,

- 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 SB2 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:

- Division of Pediatric and Maternal Health Staff (DPMH) consult request
- Current Remicade (infliximab) labeling (October 2, 2015) per Drugs@FDA
- Sponsor's proposed labeling for SB2 (March 21, 2016)
- Prior DPMH review for SB2 (IND 113461) dated May 24, 2016

2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm

Reference ID: 4084708

- Agreed upon initial Pediatric Study Plan for SB2, IND 113461 (February 3, 2016)
- Pediatric Review Committee Minutes for the November 16, 2016 meeting

Consult and Regulatory Background:

This memorandum supersedes and replaces the DPMH Pediatric Use Labeling Review memorandum dated December 16, 2016, which was prematurely finalized while still under review.

On March 31, 2016, Samsung Bioepis Co., Ltd. submitted a BLA for SB2 under the 351(k) pathway as a proposed biosimilar to Remicade (infliximab). Remicade (infliximab) 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 (TNFα) by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors.[2] 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 the following indications for which Samsung plans to seek 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 SB2, IND 113461, dated May 24, 2016.) Remicade has no outstanding pediatric postmarketing requirements and is considered fully labeled for pediatric use. However, Remicade was granted orphan designation for pediatric UC and pediatric CD, and while the orphan exclusivity for pediatric CD has expired, exclusivity for pediatric UC will not expire until September 23, 2018. Therefore, although the sponsor can submit data to fulfill the Pediatric Research Equity Act (PREA) via biosimilar extrapolation for pediatric UC, the Agency will not be able to approve SB2 for this protected indication until the orphan exclusivity expires. Of note, Inflectra (infliximab-dyyb, BLA 125544) was the first biosimilar to Remicade approved on April 5, 2016. DPARP requested DPMH-Pediatrics team assistance in providing labeling recommendations for pediatric use.

Pediatric Study Plan:

[2] Current Remicade (infliximab) labeling (October 2, 2015)

Reference ID: 4084708

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(m) 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, and a pediatric assessment is required unless waived or deferred. The Agency confirmed agreement with the agreed initial Pediatric Study Plan (iPSP) on February 3, 2016, which Samsung included in their BLA submission as their pediatric plan with no changes. Samsung proposed to demonstrate biosimilarity to Remicade and extrapolate pediatric data from Remicade based on their biosimilar development program. The agreed upon plan is summarized below, in Table 1.

Table 1. Overview of Pediatric Assessment Plan for SB2

Indication	Age	Plan for Pediatric Assessment
Juvenile Idiopathic Arthritis (JIA)	< 2	Waiver request
	2 to 4	Waiver request
	4 to 17	Extrapolation of pediatric information from the reference product
Ankylosing Spondylitis (AS)	0 to 17	Waiver request
Crohn's Disease (CD)	< 6	Waiver request
	6 to 17	Extrapolation of pediatric information from the reference product
Ulcerative Colitis (UC)	< 6	Waiver request
	6 to 17	Extrapolation of pediatric information from the reference product
Psoriatic Arthritis (PsA)	0 to 17	Waiver request
Plaque Psoriasis (PsO)	0 to 17	Waiver request

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.

DPMH Review of labeling:

The DPMH Pediatric Team labeling review will focus on edits subsection 8.4 Pediatric Use.

Pediatric Use Labeling:
The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population.

Reference ID: 4084708

When substantial evidence does not exist to support a pediatric indication, all relevant pediatric information related to the unapproved use should be restricted to the Pediatric Use subsection only, to avoid an inference of an approved pediatric indication as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. Any negative or inconclusive pediatric studies should be described in the Pediatric Use subsection, and the basis for the determination of safety and effectiveness in the pediatric population should also be provided (e.g., providing an explanation for why the available evidence does not support pediatric approval). (Also see draft Guidance for Industry and Review Staff Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, February, 2013.)

See Appendix 1 for proposed applicant labeling for SB2 dated March 21, 2016.

Discussion on Pediatric Labeling Recommendations:

Based on the biosimilar development plan, Samsung is able to extrapolate the pediatric data included throughout Remicade's labeling. Thus, SB2 labeling should incorporate similar labeling language regarding pediatric use in JIA patients 2 years and older and pediatric CD patients 6 years and older. However, SB2 will not be able to include labeling for pediatric UC until Remicade's orphan exclusivity for this indication expires. Remicade labeling for pediatric UC does not provide any safety information that is not adequately captured in the labeling for the other approved indications, which would preclude safe use if excluded. (b) (4) However, the Pediatric Research Equity Act of 2007 requires that labeling include certain information regarding the completed pediatric assessment. Therefore, a disclaimer statement should be included in the labeling stating that a pediatric assessment for SB2 demonstrates safety and effectiveness in another pediatric indication but, SB2 is not approved for such indication due to marketing exclusivity for the reference product, Remicade (infliximab).

Samsung requested a full waiver of the requirement for a pediatric assessment in PsO patients ages 0 to less than 17 years old based on safety concerns related to increased risk of malignancy and infection associated with use of TNF alpha inhibitors in children and adolescents. The Agency's current view is that this safety information does not necessarily apply across the class of TNF-alpha inhibitors, and thus would not necessarily support a waiver of the pediatric assessment for SB2 in PsO patients ages 0 to less than 17 on safety grounds. However, unlike certain other TNF-alpha inhibitors with a broader PsO indication, Remicade is approved only for treatment of adult patients with chronic severe (i.e., extensive and/or disabling) PsO who are candidates for systemic therapy and

Reference ID: 4084708

when other systemic therapies are medically less appropriate. Accordingly, a waiver of the requirement for a pediatric assessment in PsO patients ages 0 to less than 17 is justified because such studies would be impossible or highly impracticable for this narrow indication of chronic severe PsO. Note that the sponsor's proposed tradename for SB2 is Renflexis.

Conclusion:

DPMH agrees with the proposed pediatric development plans as outlined above. The PSP was reviewed by the Pediatric Review Committee on November 16, 2016, and PeRC also concurred with the proposed plan. The pediatric assessment will be deemed complete if the sponsor demonstrates biosimilarity. Therefore, no pediatric postmarketing requirements will be issued.

DPMH reviewed the applicant's draft labeling, and participated in the team meeting held on December 12, 2016. DPMH's recommended labeling for the pediatric population is provided below per 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.

DPMH Recommended Labeling for SB2:
HIGHLIGHTS OF PRESCRIBING INFORMATION

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

- **Pediatric Use – Infliximab products have not been studied in children with Crohn's disease or ulcerative colitis <6 years of age. (8.4)**

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. However, infliximab products have not been studied in children with Crohn's disease or ulcerative colitis <6 years of age.

Pediatric Crohn's Disease
RENFLEXIS 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 Warnings, Warnings and Precautions (5), Indications and Usage (1.2), Dosage and Administration (2.2), Clinical Studies (14.2) and Adverse Reactions (6.1)]*.

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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.

A pediatric assessment for RENFLEXIS demonstrates that RENFLEXIS is safe and effective in another pediatric indication. However, RENFLEXIS is not approved for such indication due to marketing exclusivity for REMICADE (infliximab).

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

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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.

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/s/

ERICA D RADDEN
04/18/2017

JOHN J ALEXANDER
04/18/2017

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

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

Memorandum

Date: April 11, 2017

To: Christine Ford, MS, RPh, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: BLA 761054
SB2, a proposed biosimilar to infliximab

OPDP acknowledges receipt of DPARP's July 28, 2016, consult request to review the proposed product labeling (package insert, carton/container labeling, and medication guide) for SB2, a proposed biosimilar to infliximab. Reference is made to DPARP's email to OPDP on March 3, 2017, conveying that a consult to OPDP is not needed at this time because this is a biosimilar, working off the Remicade USPI. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DPARP submit a new consult request during the subsequent review cycle.

If you have any questions, please contact Adewale Adeleye at 240-402-5039 or adewale.adeleye@fda.hhs.gov.

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/s/

ADEWALE A ADELEYE
04/11/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 3-30-2017

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

Through: Lynne P. Yao, M.D.
Director,
Division of Pediatric and Maternal Health

To: Division of Pulmonary, Allergy, and Rheumatology Products

Drug: Renflexis[1] (proposed biosimilar to Remicade); intravenous injection; BLA 761054

Proposed Indications: Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis,[2] rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis

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

Applicant: Samsung Bioepsis Co., Ltd.

Materials Reviewed:
- Applicant's proposed labeling and review of the literature
- Remicade approved labeling (reference listed product)
- Inflectra infliximab biosimilar approved labeling
- Literature review
- (b) (4)

[1] Proposed proprietary name.
[2] Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. Accordingly, FDA will not be able to license Renflexis for this indication until the orphan exclusivity expires.

Reference ID: 4077841

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

INTRODUCTION

This memorandum supersedes and replaces the DPMH Pregnancy and Lactation Rule (PLLR) Labeling Review memorandum dated December 16, 2016, which was prematurely finalized while still under review.

The applicant submitted a 351(k) BLA for Renflexis, a proposed biosimilar to Remicade (infliximab) on March 21, 2016. On June 23, 2016, the applicant submitted labeling in the format of the Pregnancy and Lactation Labeling Rule (PLLR) and a summary review of available pregnancy and lactation data. The proposed indications are the following:

- 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[3] :
    - 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 :

[3] This reflects information for SB2 that Samsung submitted on March 31, 2016, in its original 351(k) BLA submission. We note that the indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm

    - 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 September 15, 2016, to assist with reviewing the Pregnancy and Lactation subsections of labeling. On November 21, 2016, the applicant was sent an Information Request to submit PLLR labeling content that reflects a review of available data. The applicant submitted revised labeling on December 2, 2016.

BACKGROUND

Product Background

Remicade (infliximab) is a tumor necrosis factor (TNF) inhibitor that was approved in 1998 for treatment of Crohn's disease (CD). Remicade was subsequently approved for treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS), ulcerative colitis (UC), psoriatic arthritis, pediatric Crohn's disease, plaque psoriasis, and pediatric ulcerative colitis. Infliximab is a chimeric IgG1κ monoclonal antibody specific for human tumor necrosis factor-alpha (TNFα). Infliximab 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.

Infliximab has a molecular weight of approximately 149,100 Daltons, and the half-life is 7.7 to 9.5 days.

Inflectra, a biosimilar to US-licensed Remicade (infliximab), biosimilar manufactured by Celltrion, was approved in the U.S. on April 5, 2016.

Current state of the labeling of Remicade

Currently approved labeling of Remicade (2015) is not in the Pregnancy and Lactation Labeling Rule format. It is labeled pregnancy category B, and the Pregnancy subsection includes nonclinical data and a statement that it is not known whether Remicade can cause fetal harm. In addition, there is 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. This information is also included in Warnings and Precautions. The Nursing Mothers section includes a statement that it is not known whether Remicade is excreted in human milk or absorbed systemically and because of the potential for adverse reactions in nursing infants, women should not breastfeed.

Pregnancy and Lactation Labeling Rule (PLLR)
On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*," also known as the Pregnancy and Lactation Labeling Rule (PLLR), took effect.[4] The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule, to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW OF DATA

Pregnancy

Nonclinical Experience

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

Review of Human Pregnancy Data

Applicant's literature review

The applicant provided a summary review of published reviews on infliximab and pregnancy. A review of the applicant's summary review is provided below.

Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. (2016). "The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation". Ann Rheum Dis 75(5):795-810.

A European League Against Rheumatism (EULAR) task force was established to define points to consider on use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Based on a systematic review of the published literature (including case reports and abstracts), published and unpublished data from pregnancy registries, and data from pharmaceutical company safety databases, consensus statements on the use of antirheumatic drugs during pregnancy and lactation were developed. Based on a review of data (cutoff date of April 1, 2015) that included 1,161 documented pregnancy outcomes in patients who received infliximab products, the EULAR task force concluded that infliximab is not associated with an increased risk of congenital malformations or miscarriage. The task force concluded that infliximab can be

[4] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

continued up to gestational week 20, and if indicated, it can be used throughout pregnancy. See summary table below.

Table 1. Summary of Published Data on infliximab products in pregnancy

Studies (see Appendix 1 for references)	**N Infliximab (prospective/retrospective)**	**Number of malformations of live births (%)**	**Number of miscarriages of eligible pregnancies (%)**	**Congenital malformations (CM) and miscarriage (MC)Findings**
9 cohorts (1 abstract) 4 case controls (1 abstract) 2 register data (1 abstract) 16 case reports/series (3 abstracts)	1,161 (968/193)	20/756 (2.6%)	64/676 (9.5%)	-no difference in CM or MC

The EULAR task force publication notes that a study that showed an increased risk of birth defects following first trimester exposure to TNF α inhibitor products was published[5] after the review was completed. The authors comment that there was no pattern of malformations, and that given the absence of disease-matched controls the clinical significance of this finding is not yet clear. DPMH reviewed this publication, below.

Weber-Schoendorfer et al reported on data from a European prospective observational multi-center cohort study conducted from 1998 to 2013. Data from pregnant women exposed to aTNFα inhibitor product in the first trimester, from 11 institutions from nine countries within the European Network of Teratology Information Services were compared to data from unexposed pregnant women (healthy women not taking any teratogenic drugs). Pregnancy outcomes were available for 495 exposed women (infliximab products (n= 168), adalimumab products (n=172), etanercept products (n= 140), certolizumab products (n= 7), golimumab products (n= 3), and 1,532 unexposed women. Five patients had double exposure: infliximab products + adalimumab products (n=2), and adalimumab products + etanercept products (n=3). The study results showed that the TNFα inhibitor products exposed cohort had an increased risk for major malformations: adj OR 2.2 (95% CI 1.01, 4.8) and preterm birth: adj OR 1.69 (95% CI 1.1, 2.5) compared to the unexposed comparator. The data were adjusted for maternal age, alcohol consumption, smoking status, and number of previous pregnancies, miscarriages, and previous infants with birth defects as covariates. The study included 156 live births following infliximab products exposure. Statistical analyses were not performed for individual TNFα inhibitors products; the birth defect

[5] 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.

rate for infliximab products was 4.5%, compared with a 1.5% birth defect rate in the comparison cohort.

The risk of spontaneous abortion was not increased in the TNFα inhibitor products exposed cohort.

The authors noted that although the rate of major malformations was higher in the TNF-α inhibitor products exposed group, there was no distinct pattern of malformations. The authors acknowledged that an important limitation of the study is the lack of a disease matched comparison cohort, and that it is possible that the underlying disease activity may have contributed to the study findings.

Reviewer comments
Although the study showed an increased rate of birth defects in pregnant women treated with anti-TNF-α products, the exposed pregnancies were compared to a healthy population and not to diseased comparison group. Therefore, it is difficult to attribute the increase in birth defects to the anti-TNF-α products since disease activity and flares during pregnancy may have affected pregnancy outcomes.

The EULAR task force's review of data on 269 exposures to infliximab products in the second and third trimester showed no increase in serious infections, cognitive development or physical development at a mean follow-up time of 1.1 years. See summary table below.

Table 2. Summary of Data on exposure to infliximab products in 2nd and/or 3rd trimester

Studies (see Appendix 2 for references)	**Number of children**	**Mean follow-up time and range: years**	**Number of children vaccinated/ children with normal vaccination response**	**Rate of serious infection in 1st year of life compared to non-exposed children**	**Physical development: Number of children normal/ impaired**	**Cognitive development: Number of children normal /impaired**
2 cohort (2 abstracts) 2 case control 7 case reports	269	1.1	49/48 1 child died after BCG vaccination at 3 months of age	Not increased	57/0	22/0

Reviewer comments
With the exception of one published study (Weber-Schoendorfer), the publications that are referenced (see Appendix 1 and 2) in the EULAR taskforce review include small studies or case series with sample sizes that range from 3-86 exposures to infliximab products in pregnancy, and data reported in abstracts. The largest published study in the EULAR taskforce review includes 156 exposures to infliximab products in pregnancy (Weber-Schoendorfer study). The unpublished data that contribute to the cumulative count of over 1,000 exposures to infliximab products are not described.

The applicant provided summary information from a published review of over 1,000 exposures to infliximab products in pregnancy (includes published studies, case series and reports, and abstracts) that reported no increased risk of birth defects or miscarriage.[6] The review is based primarily on a previously published review[7], which states that the sources of data with the largest sample size of pregnant women exposed to infliximab products include the following:

- a published review of the Remicade manufacturer's safety database (n=96)[8]
- data based on the Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) Registry (n=142)[9]
- data based on the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) Pregnancy Registry (n=366 exposures to biologics; number of infliximab exposures not stated)[10].

Reviewer comment
The TREAT registry publication only reports "adverse pregnancy outcomes" as a composite rate, and does not report birth defect or miscarriage rates; therefore these data are difficult to interpret.

The applicant reviewed a publication based on a review of the FDA Adverse Events Reporting System (AERS) that describes a potential association of TNFα inhibitors with congenital anomalies consistent with the VACTERL (vertebral abnormalities, anal atresia, cardiac defect,

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[6] Ostensen M. (2014). "Safety issues of biologics in pregnant patients with rheumatic diseases". Ann N Y Acad Sci.; 1317:32-8.

[7] Nielsen, O.H., Loftus EV, Jess, T. 2013. Safety of TNF-α inhibitors during IBD pregnancy: a systematic review. BMC Med. 11: 174.

[8] Katz JA, Antoni C, Keenan GF, Smith DE, Jacobs SJ, Lichtenstein GR. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. Am J Gastroenterol 2004; 99 (12):2385–92.

[9] Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT registry. Am J Gastroenterol 2012, 107:1409–1422.

[10] Mahadevan, U. et al. 2013. Placental transfer of antitumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin. Gastroenterol. Hepatol. 11**:** 286–292.

tracheoesophageal, renal, and limb abnormalities) spectrum.[11] In the review of >120,000 adverse events reported to the FDA through December 2005, 41 children with 61 congenital anomalies were born to 40 mothers taking a TNFα inhibitor. Heart defects (n=11) were the most common congenital anomaly reported. Overall, one child was diagnosed with VACTERL, and twenty-four (59%) of the live-born infants had one or more congenital anomalies that are part of VACTERL spectrum. In 17 of the 41 cases, concomitant medications were being used by the mothers. The authors concluded that the number of congenital anomalies that are part of the VACTERL spectrum occurred at a higher rate than historical controls. However, the authors acknowledge that the potential selection bias associated with the data reported in this database, the lack of denominator data and a comparator, limit a conclusion of causality.

Reviewer comments
Subsequent to this published review of FDA AERS data, a European group conducted an independent analysis of the reported congenital anomalies, based on the case definitions of the European Surveillance of Congenital Anomalies (EUROCAT) database. The analysis found that after exclusion of 10 cases that were described as "unspecified", minor anomalies, and/or associated with a chromosomal anomaly or single gene disorder, the prevalence of major anomalies was similar to the background prevalence in the general population.[12] Furthermore, the reported anomalies in the FDA AERS database have not been corroborated in any subsequent studies or publications.

The applicant concluded that "Although current available evidence does not point to an increased risk of adverse pregnancy outcomes due to infliximab treatment, the amount of available data is still too limited to definitively exclude this risk."

Reviewer comment
DPMH concurs with this assessment.

DPMH Literature Review
In addition to the data reviewed by the applicant, this reviewer identified another published study on exposure to infliximab products in pregnancy, described below.

A retrospective cohort study of 156 exposures to infliximab products using Danish and Swedish population-based health registers showed no increased risk for major malformations compared to a disease matched cohort.[13]

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[11] Carter JD, Valeriano J, Vasey FB (2006) Tumor necrosis factor-alpha inhibition and VATER association: a causal relationship. J Rheumatol. 33(5):1014–1017.

[12] Crijns HJN, Jentink J, Garne E, et al. The Distribution of Congenital Anomalies Within the VACTERL Association Among Tumor Necrosis Factor Antagonist-exposed Pregnancies Is Similar to the General Population. J Rheumatol 2011;38;1871-1874.

[13] Broms G, Grantah F, Ekbom A, et al. Low Risk of Birth Defects for Infants whose mothers are treated with Anti-Tumor Necrosis Factor Agents During Pregnancy. Clinical Gastroenterology and Hepatology 2016; 14:234-241.

Clinical Guidelines
The European League Against Rheumatism taskforce states that infliximab can be continued up to gestational week 20, and if indicated, it can be used throughout pregnancy.

The World Congress of Gastroenterology has stated that "Infliximab in pregnancy is considered to be low risk and compatible with use during conception in men and women and during pregnancy in at least the first two trimesters."[14]

Review of Pharmacovigilance Database
One pregnancy occurred during the clinical development program; the outcome was a full term pregnancy with no birth defects.

(b) (5)

[redacted]

Summary
Published reviews conclude that infliximab products are not associated with an increased risk of major malformations or miscarriage based on over 1,000 pregnancy exposures to infliximab products. However, most of these data are based on small cohorts and data that have not been reviewed in the peer literature. The largest published studies consist of a Danish-Swedish retrospective cohort study that includes 156 exposures (Broms 2016), and a European prospective cohort study that includes 168 exposures (Weber-Schondorfer 2015). The Broms study showed no increased risk of major malformations. The Weber-Schondorfer study showed an increased risk of major malformations and preterm birth; however, there was no distinct pattern of malformations and study results may have been confounded by the underlying disease, as the comparator group was a healthy cohort.

Based on available published epidemiologic studies of cohorts that include over 100 exposures to infliximab products during the first trimester of pregnancy, data have not shown a consistent association with specific malformations or a pattern of malformations. The data on the risk of miscarriage and preterm birth following fetal exposure to infliximab products are limited, and not sufficient to draw conclusions. (b) (5)

[redacted]

[14] Mahadevan U, Cucchiara S, Hyams JS, Steinwurz F, Nuti F, Travis SP, Sandborn WJ, Colombel JF. (2011). "The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD With the European Crohn' s and Colitis Organization: Pregnancy and Pediatrics". Am J Gastroenterol 106(2):214-23.

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

Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. (2016). "The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation". Ann Rheum Dis 75(5):795-810.

Based on a systematic literature review, the EULAR taskforce identified a total of 25 case reports that report on infliximab products and breastfeeding, including 17 cases that identified low levels of infliximab products in milk, and 5 cases that did not detect infliximab products in milk (see Appendix 3 for reference list). There was one case report that detected low infliximab product infant serum levels, and 2 cases that did not detect infliximab products in infant serum. No adverse events were reported. The taskforce concluded that absorption is unlikely due to low bioavailability, and that infliximab is compatible with breastfeeding.

Clinical Guidelines

The European League Against Rheumatism taskforce and the World Congress of Gastroenterology (WCOG) have stated that infliximab is compatible with breastfeeding.

Review of Pharmacovigilance Database

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

The applicant concludes that "No adverse events have been reported as a result of infliximab transferred by breastfeeding and current evidence suggests that use of infliximab is compatible with breastfeeding."

DPMH Literature Review

DPMH conducted a search of *Medications and Mother's Milk*[15], the Drugs and Lactation Database (LactMed),[16]and of published literature in PubMed and Embase using the search terms "infliximab and lactation" and "infliximab and breastfeeding."

[15] Hale, Thomas (2017) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing.

[16] 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 geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal 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.

In *Medications and Mother's Milk,* Thomas Hale, a breastfeeding expert, states the following regarding infliximab and lactation:

"Limited data. The amount in breastmilk is very low; probably compatible with breastfeeding. There are no long term safety data; some caution is recommended."

Infliximab is referenced in LactMed. The Summary of Use states:

"Infliximab is usually not detectable in breastmilk and absorption is unlikely because it is probably destroyed in the infant's gastrointestinal tract".

DPMH reviewed the case series reported in the literature, below. These publications are referenced in the EULAR taskforce report.

Three women with Crohn's disease who were at least 5 days postpartum received an intravenous infusion of infliximab 5 mg/kg for a disease flare and discontinued nursing.[17] Milk samples were obtained before and after the infusion. Infliximab was not detectable (<10 mcg/L) in all of the pre-infusion samples. Infliximab was detectable 12 hours after the infusion and peaked at 90 to 105 mcg/L at 2 to 3 days after the infusion in 2 patients. Milk levels corresponded to 0.5% of the levels in maternal serum. In a third, one sample obtained 2 days after the infusion was about 20 mcg/L. The authors concluded that infliximab is excreted in breastmilk in miniscule amount.

A study was conducted in three women with Crohn's disease who received infliximab during pregnancy and postpartum.[18] In two women, infliximab was discontinued at or before 32 weeks of pregnancy and restarted within 2 weeks postpartum. Single breastmilk samples were obtained 5 and 7 days after a postpartum dose of 5 mg/kg of infliximab. Infliximab was undetectable (<100 mcg/L) in both breastmilk samples. An infant serum sample that was obtained 5 days after the mother's infliximab dose in one infant that was 15 days old, was found to be undetectable. In one woman who received her last infliximab dose at 25 weeks, and restarted 2 weeks postpartum, both milk and infant serum concentrations were undetectable 43 days after the mother's dose at 57 days of age. No adverse reactions were observed in any of the infants. Infants were followed for almost a year and found to have no unusual number or types of infections and all seroconverted after their routine childhood immunizations.

A study was conducted in two mothers who received infliximab product 300 mg intravenously for inflammatory bowel disease.[19] In one mother who was 34 weeks postpartum, the infliximab product milk level 3 weeks after the last infusion was 200 mcg/L, which was about 5% of her serum concentration. Infliximab product was undetectable in the infant's serum. The second mother began infliximab product at 3 months postpartum. Her breastmilk infliximab product

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[17] Ben-Horin S, Yavzori M, Kopylov U et al. Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. J Crohns Colitis. 2011;5:555-8.

[18] Kane S, Ford J, Cohen R, Wagner C. Absence of infliximab in infants and breast milk from nursing mothers receiving therapy for Crohn's disease before and after delivery. J Clin Gastroenterol. 2009;43:613-6.

[19] Fritzsche J, Pilch A, Mury D et al. Infliximab and adalimumab use during breastfeeding. J Clin Gastroenterol. 2012;46:718-9.

levels were 94.6 mcg/L and 119.7 mcg/L on day 1 and 4 after the dose. Four weeks later she received a second dose of infliximab product. Five days after the second dose, her infant had a serum concentration of 1.7 mcg/L, which was 2.2% of the maternal serum infliximab product concentration. In both of these no adverse events were reported and the infants reached their developmental milestones at 18 and 22 months. The authors note that this is the only report in the literature that documents the presence of infliximab in infant serum and that it is not clear whether transplacental passage may have contributed to the finding (the timing of the last dose administered during pregnancy is not stated).

Reviewer comment
Because infliximab has been detected in infant serum up to 6 months following birth (as described in Remicade labeling), it is not clear whether transplacental passage contributed to the presence of infliximab product in the infant's serum.

An abstract reported on 11 women who received infliximab (dose unspecified) as part of the PIANO Pregnancy Registry submitted breastmilk samples.[20] Samples were taken at 1, 12, 24 and 48 hours after drug administration any time after delivery. Infliximab was detected in breastmilk at levels between 90 and 591 mcg/L between 24 and 48 hours after infusion. Infant follow up data were pooled for all TNF α inhibitors. Mean infant weight and height increase in the first year did not differ based on in utero drug exposure, third trimester exposure, or breastfeeding. Infant milestone achievement at 4, 9 and 12 months was similar in all groups regardless of breastfeeding status. Breastfed infants with and without 3rd trimester or postpartum drug exposure had similar rates of milestone achievement at 1 year. Infection rates at months 4, 9 and 12 were similar among breastfed infants exposed and unexposed to any medical therapy.

Summary
Available data show that infliximab product levels in milk are low, and the amount that a breastfeeding infant would be exposed to is substantially less than the limit of 10% of the maternal weight adjusted dose that is accepted as the safety threshold by lactation experts.[21] However available data are based on a limited number of case reports following single dose administration at various times following the infusion. Therefore it is not possible to draw conclusions based on 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.

[20] Matro R, Martin CF, Wolf DC et al. Detection of biologic agents in breast milk and implication for infection, growth and development in infants born to women with inflammatory bowel disease: Results from the PIANO registry. Gastroenterology. 2015;148:S141. Abstract.

[21] Anderson PO. What do all the numbers mean? Breastfeeding Medicine 2016 (11);6; 277-279.

Review of Data

Applicant's Literature Review

The applicant did not identify any published human data on infertility effects in female patients following exposure to infliximab.

In a prospective study of 10 men with inflammatory bowel disease (IBD), semen analysis was performed prior to infliximab infusion and 1 week after infusion. Seven men were in remission and on maintenance infliximab (group 1) and 3 were receiving a first dose for moderate or severe disease (group 2).[22] The study results showed that all 10 patients had low normal oval forms prior to infusion, and group 1 had a significant decrease in the percentage of normal oval forms after infusion. No other abnormalities were seen. The authors concluded it is not known if the semen analysis findings translate into impaired fertility and therefore they do not recommend that men receiving infliximab stop therapy if they are considering conception.

In a prospective study, 20 male patients (average age 34) with ankylosing spondylitis (AS) and taking anti-TNF therapy (infliximab product 5 mg/kg every 8 weeks (n=4), adalimumab product 40 mg every 2 weeks (n=14), etanercept product 50 mg every week (n=2)) were compared to 42 controls of healthy males (average age 34).[23] The patients in the treatment group gave semen samples once before the start of anti-TNF therapy. The second semen analysis occurred three to six months after the start of anti-TNF therapy (n=20 patients) and a third semen analysis was performed at 12- months after the start of anti-TNF therapy (n=6 patients). At baseline and at 3-6 months, 91% of the males in the treatment group had normospermia and 9% had oligospermia. At the 12-month follow-up, 100% of the patients had normospermia and none of the patients had oligospermia; out of the six patients who followed up at 12-months, one was on an infliximab product and five were on an adalimumab product. There was no statistically significant difference in sperm quality between patients in the treatment group and the control group. The authors concluded that the disease process of AS and exposure to anti-TNF therapy do not appear to adversely affect sperm quality during active phases of AS.

In a prospective study, 10 male patients with spondyloarthritis (SpA) had semen and reproductive lab parameters compared with 20 healthy control subjects.[24] The treatment group had a semen evaluation before and after one year of treatment with adalimumab products (40 mg every two weeks for 12-months). The average age of patients was 28 (age 27 in controls). At baseline, the subjects in the treatment group had lower sperm motility, higher luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels, and lower testosterone levels than the control group. After treatment with adalimumab products, there was a statistically significant improvement in sperm motility, hormone levels, and sperm aneuploidies. The authors concluded that the study hypothesizes that inflammatory diseases, such as SpA, can affect sperm quality

[22] Mahadevan U, Terdiman JP, et al. Infliximab and Semen Quality in Men with Inflammatory Bowel Disease. Inflamm Bowel Dis 2005; 11(4):395-399.

[23] Micu, et al. TNF-a inhibitors do not impair sperm quality in males with ankylosing spondylitis after short term or long-term treatment. Rheumatology. 2014; 53(7):1250-5.

[24] Ramonda, et al. Influence of tumor necrosis factor α inhibitors on testicular function and semen in spondyloarthritis patients. Fertil Steril. 2014: 101(2): 359-365.

Reference ID: 4077841

and sex hormone levels and that anti-TNF therapy may actually improve testicular function or spermatogenesis.

In a prospective cohort study of 26 male patients with SpA (11 patients not currently on anti-TNF therapy and 15 patients on long-standing TNF therapy, including 16 men who received infliximab), semen samples were compared with 102 healthy male subjects.[25] The authors found that the 11 patients with SpA who were untreated had poorer sperm motility and vitality compared to the 15 patients with SpA who were on treatment. There was no difference in sperm quality between healthy controls and the anti-TNF treated patients.

The applicant concluded that due to the limitations of currently available data, it is not known if infliximab has an effect on infertility.

DPMH Literature Review
DPMH performed a search of published literature on infliximab and infertility and did not identify any additional publications.

Summary
Animal reproductive studies of administration of infliximab did not show any adverse effects on fertility. 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 Renflexis labeling.

DISCUSSION

Pregnancy

The applicant's proposed labeling language that states that limited published data on use of infliximab in pregnant women are insufficient to inform a drug associated risk, and that published studies with infliximab use during pregnancy have not reported a clear association with infliximab and adverse pregnancy outcomes, is consistent with DPMH's assessment.

(b) (4) As these data have not been reviewed by the Agency, they cannot be included in labeling at the present time. (b) (4), (b) (5) Addition of human data to labeling is deferred, pending review of these data.

[25] Villiger, et al. Effects of TNF antagonists on sperm characteristics in patients with spondyloarthritis. Annals of Rheumatic Disease. 2010. 69(10): 1842-4.

Lactation

The applicant's proposed labeling language, [redacted (b) (4)]. DPMH recommends not including such a statement in Renflexis labeling, [redacted (b) (4)]. [redacted (b) (4)] it is our view that these data are not appropriate to include in labeling. Available published case reports are not sufficient to draw conclusions on the level of inflimab products in human milk. [redacted (b) (4)]. In addition, DPMH recommends that the following risk/benefit statement be included under the Risk Summary heading:

The development 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.

CONCLUSION

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

- **8.1 Pregnancy**
  - The "Pregnancy" subsection of Renflexis 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 Renflexis labeling was formatted in the PLLR format to include the "Risk Summary" and "Data" sections.

DPMH LABELING RECOMMENDATIONS[26]

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

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26 [redacted (b) (5)]

maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα *[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, 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)]*.

Data

Animal Data

Because infliximab products do not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with infliximab products. No evidence of maternal toxicity or embryotoxicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies.

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.

Appendix 1-References cited by EULAR review of infliximab exposure in pregnancy

Cooper WO, Cheetham TC, Li DK, et al. Brief report: risk of adverse fetal outcomes associated with immunosuppressive medications for chronic immune-mediated diseases in pregnancy. Lupus 2014;66:444–50.

Casanova MJ, Chaparro M, Domènech E, et al. Safety of thiopurines and anti-TNF-α drugs during pregnancy in patients with inflammatory bowel disease. Am J Gastroenterol 2013; 108:433–40.

Bortlik M, Machkova N, Duricova D, et al. Pregnancy and newborn outcome of mothers with inflammatory bowel diseases exposed to anti-TNF-α therapy during pregnancy: three-center study. Scand J Gastroenterol 2013;48:951–8.

Diav-Citrin O, Otcheretianski-Volodarsky A, Shechtman S, et al. Pregnancy outcome following gestational exposure to TNF-alpha-inhibitors: a prospective, comparative, observational study. Reprod Toxicol 2014;43:78–84.

Giacuzzo S, Padovan M, Capucci R, et al. Pregnancy outcome of mothers with rheumatic diseases exposed to biological agent during pregnancy: a single-centre study. Ann Rheum Dis 2014;73(Suppl 2):414.

Kalari S, Granath F, Guo CY, et al. Pregnancy outcomes in women with rheumatologic conditions exposed to infliximab. Ann Rheum Dis 2014;73 (Suppl 2):482–3.

Kelly O, Hartery K, Boland K, et al. TNF alpha inhibitor use in pregnancy: Experience in a European cohort. J Crohn's Colitis 2014; 8:S204–S05.

Mahadevan U, Wolf DC, Dubinsky M, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2013;11:286–92.

Schnitzler F, Fidder H, Ferrante M, et al. Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. Inflamm Bowel Dis 2011;17:1846–54.

Seirafi M, de Vroey, B, Amiot A, et al. Factors associated with pregnancy outcome in anti-TNF treated women with inflammatory bowel disease. Aliment Pharmacol Ther 2014;40:363–73.

Verstappen SM, King Y, Watson KD, et al. Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2011;70:823–6.

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.

Zelinkova Z, van der Ent C, Bruin KF, et al. Effects of discontinuing anti-tumor necrosis factor therapy during pregnancy on the course of inflammatory bowel disease and neonatal exposure. Clin Gastroenterol Hepatol 2013;11:318–21.

Reference ID: 4077841

Appendix 2-References cited by EULAR review of infliximab exposure in 2nd and 3rd trimester of pregnancy

Bortlik, M, Duricova, D, Machkova, N, et al. Impact of anti-tumor necrosis factor alpha antibodies administered to pregnant women with inflammatory bowel disease on long-term outcome of exposed children. Inflamm Bowel Dis 2014;20:495-501.

Cheent, K, Nolan, J, Shariq, S, et al. Case Report: Fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's Disease. Journal of Crohn's and Colitis 2010;4:603-05.

Correia, LM, Bonilha, DQ, Ramos, JD, et al. Inflammatory bowel disease and pregnancy: Report of two cases treated with infliximab and a review of the literature. Eur J Gastroenterol Hepatol 2010;22:1260-64.

Fritzsche, J, Pilch, A, Mury, D, et al. Infliximab and adalimumab use during breastfeeding. J Clin Gastroenterol 2012;46:718-9.

Guiddir, T, Fremond, ML, Triki, TB, et al. Anti-TNF-alpha therapy may cause neonatal neutropenia. Pediatrics 2014;134:e1189-93.

Kane, S, Ford, J, Cohen, R, et al. Absence of infliximab in infants and breast milk from nursing mothers receiving therapy for Crohn's disease before and after delivery. J Clin Gastroenterol 2009;43:613-6.

Mahadevan, U, Martin, CF, Chambers, C, et al. Achievement of developmental milestones among offspring of women with inflammatory bowel disease: The piano registry. [abstract].Gastroenterology 2014;1(Suppl 5):S1.

Mahadevan, U, Martin, CF, Dubinsky, M, et al. Exposure to anti-TNFalpha therapy in the third trimester of pregnancy is not associated with increased adverse outcomes: Results from the piano registry. [abstract].Gastroenterology 2014;1(Suppl 5):S170.

Seirafi, M, de Vroey, B, Amiot, A, et al. Factors associated with pregnancy outcome in anti-TNF treated women with inflammatory bowel disease. Aliment Pharmacol Ther 2014;40:363-73.

Steenholdt, C, Al-Khalaf, M, Ainsworth, MA, et al. Therapeutic infliximab drug level in a child born to a woman with ulcerative colitis treated until gestation week 31. Journal of Crohn's and Colitis 2012;6:358-61.

Stengel, JZ, Arnold, HL. Is infliximab safe to use while breastfeeding? World J Gastroenterol 2008;14:3085-87.

Appendix 3-References cited by EULAR review of infliximab exposure in lactation

Ben-Horin, S, Yavzori, M, Kopylov, U*, et al.* Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. *J Crohns Colitis* 2011;5:555-8.

Correia, LM, Bonilha, DQ, Ramos, JD*, et al.* Inflammatory bowel disease and pregnancy: Report of two cases treated with infliximab and a review of the literature. *Eur J Gastroenterol Hepatol* 2010;22:1260-64.

Fritzsche, J, Pilch, A, Mury, D*, et al.* Infliximab and adalimumab use during breastfeeding. *J Clin Gastroenterol* 2012;46:718-9.

Grosen, A, Julsgaard, M, Kelsen, J*, et al.* Infliximab concentrations in the milk of nursing mothers with inflammatory bowel disease. *J Crohns Colitis* 2014;8:175-6.

Kane, S, Ford, J, Cohen, R*, et al.* Absence of infliximab in infants and breast milk from nursing mothers receiving therapy for Crohn's disease before and after delivery. *J Clin Gastroenterol* 2009;43:613-6.

Matro, R, Martin, CF, Wolf, DC*, et al.* Detection of biologic agents in breast milk and implication for infection, growth and development in infants born to women with inflammatory bowel disease: Results from the piano registry. [*abstract*].*Gastroenterology* 2015;1(Suppl 4):S141.

Stengel, JZ, Arnold, HL. Is infliximab safe to use while breastfeeding? *World J Gastroenterol* 2008;14:3085-87.

Tursi, A. Effect of intentional infliximab use throughout pregnancy in inducing and maintaining remission in Crohn's disease. *Dig Liver Dis* 2006;38:439-40.

Vasiliauskas, EA, Church, JA, Silverman, N*, et al.* Case report: evidence for transplacental transfer of maternally administered infliximab to the newborn. Clin Gastroenterol Hepatol 2006;4:1255-8.

Reference ID: 4077841

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LEYLA SAHIN
03/30/2017

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03/31/2017

Clinical Inspection Summary (Addendum) DRAFT

Date	January 12, 2017
From	Janice Pohlman, M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation
To	Juwaria Waheed, M.D., DPARP, Medical Officer Nikolay Nikolov, DPARP, Cross-Discipline Team Leader Christine Ford, M.S., R.Ph., Regulatory Project Manager Division of Pulmonary, Allergy and Rheumatology Products
NDA/BLA #	BLA 761054
Applicant	Samsung Bioepis Co., Ltd.
Drug	SB2, infliximab, a biosimilar to approved Remicade®
NME (Yes/No)	No
Therapeutic Classification	Biosimilar 351(k)
Proposed Indication(s)	Rheumatoid arthritis in combination with methotrexate; ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's Disease, pediatric Crohn's Disease, ulcerative colitis, and pediatric ulcerative colitis
Consultation Request Date	June 23, 2016 (signed)
Summary Goal Date	Extended: December 9, 2016
Action Goal Date	January 20, 2017
PDUFA Date	January 21, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based upon FDA inspections of two clinical investigator (CI) sites (sample of enrolling sites) and the clinical trial records maintained by the sponsor's US Agent/monitoring CRO, Quintiles, for Study SB2-G31-RA, it is our conclusion that the study appears to have been conducted and monitored adequately and that the data reported by the sponsor to the BLA (based upon verification of data from the two inspected CI sites) is reliable to be used in support of the indication.

Reports from the European Medicines Agency (EMA) inspections are provided by EMA to FDA in accordance with confidentiality agreements and are provided as information for the review division to consider potential significance as it relates to their study analyses.

II. BACKGROUND

The Clinical Inspection Summary (CIS) for this application was entered into DARRTS on December 9, 2016. The summary contained information about FDA inspections conducted at two CI sites and a sponsor inspection conducted at the sponsor's U.S. agent facility for Study SB2-G31-RA. One of the two clinical investigator sites (Site SB21403) was issued a Form FDA 483, Inspectional Observations for failure to conduct the study according to the investigational plan. The other CI site (Site SB21012) and the sponsor inspection conducted at the U.S. Agent's location received a final classification of No Action Indicated (NAI). Following completion of the CIS on December 9, 2016, the inspection report for Site SB21403 was received from the Office of Regulatory Affairs; based upon review of that report, the preliminary classification of that inspection remains Voluntary Action Indicated (VAI) and the classification will be finalized upon issuance of correspondence to the inspected entity.

In addition to information related to FDA inspections, the CIS contained EMA inspection reports provided by EMA and shared with FDA under the confidentiality agreements between the two regulatory authorities. (b) (4) Detailed EMA inspection findings are not made publically available at this time. As was noted in the original CIS, the EMA inspection summary indicated (b) (4)

For full details related to the inspections, please see the CIS entered into DARRTS on December 9, 2016.

III. RESULTS (by site):

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Date	Classification
Nenad Prodanovic, M.D., Ph.D. Clinical Center Banja Luka Ulica 12 Beba bb Banja Luka, 78000 Bosnia and Herzegovina	Protocol SB2-G31-RA Site #SB21403 31 subjects randomized	September 5 – 9, 2016	Pending: Preliminary VAI
Jaroslaw Niebrzydowski, M.D. Medica Pro Familia ul. Chrzanowskiego 3/5 Gdynia, 81-338, Poland	Protocol SB2-G31-RA Site #SB21012 30 subjects randomized	October 10-14, 2016	NAI
Quintiles, Inc. Sponsor's U.S. Agent for Samsung Bioepis Co., Ltd. 4820 Emperor Blvd. Durham, NC 27703	Protocol SB2-G31-RA (Quintiles, Mumbai, India responsible for monitoring and data management)	August 2-5, 2016	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has been received from the field and reviewed. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

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Janice Pohlman, M.D., M.P.H.
Team Leader
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Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H.
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Central Doc. Rm.
DPARP/Division Director/Badrul Chowhury
DPARP/Medical Team Leader/Nikolay Nikolov
DPARP/Project Manager/Christine Ford
DPARP/Medical Officer/Juwaria Waheed
OCC/Joseph Franklin
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Janice Pohlman
OSI/DCCE/GCP Reviewer/Anthony Orencis
OSI/ GCP Program Analyst/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

JANICE K POHLMAN
01/12/2017

KASSA AYALEW
01/12/2017

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:	December 20, 2016
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761054
Product Name and Strength:	Renflexis (SB2)* For Injection 100 mg per vial
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Samsung Bioepis
Submission Date:	March 21, 2016
OSE RCM #:	2016-747
DMEPA Primary Reviewer:	Matthew Barlow, RN, BSN
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH
DMEPA Deputy Director:	Lubna Merchant, MS, PharmD

* Renflexis has been developed as a proposed biosimilar to US-licensed Remicade (infliximab). Since the proper name for Renflexis has not yet been determined, SB2 is used throughout this review in place of the nonproprietary name for this product

Reference ID: 4031165

1 REASON FOR REVIEW

This review evaluates the applicant's proposed Prescribing Information (PI), carton labeling, and container label for Renflexis (SB2) * for injection (BLA 761054) for areas of vulnerability that may lead to medication errors. The Division of Pulmonary, Allergy, and Rheumatology (DPARP) requested this review to inform their evaluation of the 351(k) BLA submission for Renflexis. US-licensed Remicade (BLA 103772), was approved on August 24, 1998.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed container label, carton labeling, and Prescribing Information for Renflexis (SB2)* to determine whether there are significant concerns in terms of safety, related to preventable medication errors. We identified areas of the proposed labels and labeling that could be revised to improve clarity and readability of important information. We note the strength and proprietary name, storage information, and reconstitution instructions can be revised to increase the prominence and clarity of this information. We contacted the Office of Biologic Products (OBP) regarding the proposed labels and labeling and discussed the recommendations for the proposed labels and labeling of this product. OBP provided recommendations to create space on the container label which are included in section 4.1.

* Renflexis has been developed as a proposed biosimilar to US-licensed Remicade (infliximab). Since the proper name for Renflexis has not yet been determined, SB2 is used throughout this review in place of the nonproprietary name for this product

Reference ID: 4031165

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. We provide recommendations for Samsung Bioepis in Section 4.1, to be implemented prior to approval of BLA 761054.

4.1 RECOMMENDATIONS FOR SAMSUNG BIOEPIS

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

A. Carton Labeling and Container Label
    1. Revise the strength statement throughout the carton labeling and container label (including the statement in the green box) to "100 mg per vial."
    2. Revise the storage statement to as follows: "Must be refrigerated, store at 2°C to 8°C (36°F to 46°F)". Additionally, we recommend bolding this statement to increase the prominence of this important information and minimize the risk of the storage information being overlooked.
    3. Replace the placeholder "NDC XXXXX-XXX-XX" with the product NDC number.

B. Container Label
    1. Re-locate the 'Rx only' statement to be placed after the statements "Single-dose vial. Discard unused portion."
    2. Include the following statement on the middle panel of the label to ensure proper preparation and administration of this product: "Must reconstitute and dilute before intravenous infusion. Must infuse over at least 2 hours with an in-line filter."
    3. Include the statement "Usual Dosage: See Prescribing Information" to ensure proper preparation and administration of this product.
    4. Add the product barcode to the container label as required per 21 CFR 201.25(c)(2). The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore it is an important safety feature that should be part of the label whenever possible. Additionally, consider orienting the barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature.
    5. To create space on the partial label (21 CFR 610.60(c)), consider deleting the following information that is not required on the partial label:
        i. (b) (4)
        ii.
        iii.

Reference ID: 4031165

C. Carton Labeling

1. Revise the [redacted] font used on the carton labeling for the product name and strength to a darker color to improve contrast and readability. As currently presented, the contrast between the [redacted] font and white background makes the information difficult to read.
2. Include the following statement on the Principal Display Panel (PDP) in bold font to ensure the proper preparation and administration of the product: "Must reconstitute and dilute before intravenous infusion. Must infuse over at least 2 hours with an in-line filter."
3. To allow for the above recommendation, consider removing the statement, "[redacted]." from the PDP as this information is on the side panel.
4. To ensure the proper preparation of the product, revise the statement on the side panel, [redacted] to as follows:
   "Reconstitute each vial with 10 mL Sterile Water for Injection, USP. Do NOT shake reconstituted solution. Must further dilute with 0.9% Sodium Chloride, USP. Once reconstituted, each mL contains…"
5. Revise the statement "[redacted]" to read "Usual Dosage: See Prescribing Information."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Renflexis (SB2)* that Samsung Bioepis submitted on March 21, 2016, and US-licensed Remicade (BLA 103772).

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

Product Name	**Renflexis**	**US-licensed Remicade**
Initial Approval Date	N/A	August 24, 1998
Active Ingredient	SB2*	Infliximab
Indication	• Crohn's Disease • Pediatric Crohn's Disease • Ulcerative Colitis • Rheumatoid Arthritis in combination with methotrexate • Ankylosing Spondylitis • Psoriatic Arthritis • Plaque Psoriasis	• Crohn's Disease • Pediatric Crohn's Disease • Ulcerative Colitis • Pediatric Ulcerative Colitis • Rheumatoid Arthritis in combination with methotrexate • Ankylosing Spondylitis • Psoriatic Arthritis • Plaque Psoriasis
Route of Administration	Intravenous Infusion	Intravenous Infusion
Dosage Form	For injection (Lyophilized Powder for Reconstitution)	For injection (Lyophilized Powder for Reconstitution)
Strength	100 mg/Vial	100 mg/Vial
Dose and Frequency	**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. **Rheumatoid Arthritis:** In	**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

* Renflexis has been developed as a proposed biosimilar to US-licensed Remicade (infliximab). Since the proper name for Renflexis has not yet been determined, SB2 is used throughout this review in place of the nonproprietary name for this product

	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.	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. Dependent on Indication (See Above)
How Supplied	Each RENFLEXIS 100 mg vial is individually packaged in a carton. Each single dose vial contains 100 mg of infliximab for final reconstitution volume of 10 mL.	Each REMICADE 100 mg vial is individually packaged in a carton. REMICADE is supplied in an accumulator carton containing 10 vials. Each single dose vial contains 100 mg of infliximab for final reconstitution volume of 10 mL.
Storage	RENFLEXIS must be refrigerated at 2°C to 8°C (36°F to 46°F).	REMICADE must be refrigerated at 2°C to 8°C (36°F to 46°F).

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On September 20, 2016, we searched the L:drive and AIMS using the terms, Renflexis and SB2*, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous reviews related to the labels and labeling of this product.

APPENDIX C. HUMAN FACTORS STUDY—N/A

APPENDIX D. ISMP NEWSLETTERS—N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)—N/A

APPENDIX F. OTHER—N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Renflexis labels and labeling submitted by Samsung Bioepis on March 21, 2016.

- Container label
- Carton labeling
- Prescribing Information

G.2 Label and Labeling Images

A. Container Label

(b) (4)

B. Carton Labeling

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

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/s/

MATTHEW J BARLOW
12/20/2016

MISHALE P MISTRY
12/20/2016

LUBNA A MERCHANT
12/21/2016

CLINICAL INSPECTION SUMMARY

Date	December 9, 2016
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Janice Pohlman M.D., M.P.H., GCPAB Team Leader Susan D. Thompson, M.D. ,GCPAB Team Leader and Acting Branch Chief for Kassa Ayalew, M.D., M.P.H. GCPAB Branch Chief Division of Clinical Compliance Evaluation/OSI
To	Juwaria Waheed, M.D., DPARP, Medical Officer Nikolay Nikolov, DPARP, Cross-Discipline Team Leader Christine Ford, M.S., R.Ph., Regulatory Project Manager Division of Pulmonary, Allergy and Rheumatology Products
NDA	BLA 761054
Applicant	Samsung Bioepis Co., Ltd.
Drug	SB2, infliximab, a biosimilar to approved drug Remicade®
NME	No
Therapeutic Classification	Biosimilar 351(k)
Proposed Indication	Rheumatoid arthritis in combination with methotrexate; ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's Disease, pediatric Crohn's Disease, ulcerative colitis, and pediatric ulcerative colitis
Consultation Request Date	June 23, 2016 (signed)
Summary Goal Date	Extended: December 9, 2016
Action Goal Date	January 20, 2017
PDUFA Date	January 21, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The sponsor's U.S. agent for this application, Quintiles, and two foreign clinical sites (Drs. Prodanovic and Niebrzdowski) were inspected as requested by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). The final CDER regulatory classification of the CRO monitoring site (Quintiles) and Dr. Niebrzdowski's clinical site is No Action Indicated (NAI).

The preliminary regulatory classification of Dr. Prodanovic's site is Voluntary Action Indicated (VAI) based on communications with the field investigator. At this site, the independent joint assessor (IJA) appeared to have also participated in completing additional assessment forms used as subcomponents of the efficacy endpoint for ten out of 31 subjects randomized. Nine of the ten

subjects who were found to have multiple visits (i.e. three to four), where the IJA may have completed both activities included the Baseline assessment against which the Visit 6 assessments would be compared, for determination of efficacy. Although there is potential for biased assessment of joint findings (or recording of subject global assessment and disability scores by the IJA, depending upon the order of procedure completion) the extent of the IJA's contribution is unclear based upon preliminary communications. Therefore, any potential impact on the efficacy endpoint (i.e. ≥ 20% reduction in American College of Rheumatology (ACR) 20) at Visit 6, relative to Visit 1, Baseline) should be mitigated by randomization.

Observations related to the inspection at Dr. Prodanovic's site are preliminary and a clinical inspection summary addendum will be provided to the review division should recommendations change based upon review of the final inspection report.

2. BACKGROUND

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity, avidity and specificity, to both the soluble and transmembrane forms of TNF-α, but which does not cross-react with TNF-β. Treatment with infliximab has been shown to reduce levels of other cytokines and markers of inflammation, including interleukin-6 and C-reactive protein.

A single randomized clinical trial was submitted in support of the applicant's BLA for the treatment of rheumatoid arthritis (RA) despite methotrexate (MTX) therapy, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's Disease, pediatric Crohn's Disease, ulcerative colitis, and pediatric ulcerative colitis. To demonstrate equivalence of SB2 (infliximab), a biosimilar to Remicade®, the submitted clinical trial compared SB2 to European Union sourced Remicade® for treatment of adult patients with moderate to severe RA despite methotrexate therapy.

For this 351k (biosimilar) BLA, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested two foreign clinical sites for inspection. These sites principally enrolled large numbers of study subjects and had high subject drop out, protocol violations, or other study risk considerations identified by the review division. The CRO, Quintiles, was contracted for site monitoring and data management for the clinical study and as the U.S. agent representing the sponsor. The CRO was engaged (in lieu of the sponsor) to assess conduct and oversight of the clinical study submitted to support approval of this BLA.

Study Protocol SB2-G31-RA

Study SB2-G31-RA was a randomized, double-blind, parallel group, multicenter clinical study. Subjects with moderate to severe RA with an inadequate response to MTX were randomized in a 1:1 ratio to receive either SB2 3 mg/kg or European Union (EU) sourced Remicade® 3 mg/kg.

The objective of the study was to demonstrate the equivalence of SB2 to Remicade® at Week 30, in subjects with moderate to severe RA receiving methotrexate therapy.

The primary efficacy endpoint for the RA indication was the American College of Rheumatology (ACR) 20% response criteria, response rate at Week 30.

This multicenter study was conducted at 73 centers worldwide. A total of 584 subjects were randomized to the following treatment groups: SB2 3 mg/kg (n = 291) or European Union sourced Remicade® 3 mg/kg (n=293). The first study subject signed the informed consent on August 12, 2013.
The 54-week data cut-off date was March 4, 2015.

Per sponsor submission to the agency, the ACR20 response rate at Week 30 was equivalent in the SB2 and Remicade® treatment groups. In the sponsor's statistical analysis, the adjusted treatment difference was contained within the pre-defined equivalence margin of [−15%, 15%].

3. RESULTS (by site):

Name of Sponsor, Address	Protocol # / Site # / # randomized	Inspection Date	Classification
Nenad Prodanovic, M.D., Ph.D. Clinical Center Banja Luka Ulica 12 Beba bb Banja Luka, 78000 Bosnia and Herzegovina	Protocol SB2-G31-RA Site #SB21403 31 subjects randomized	September 5 – 9, 2016	Pending: Preliminary VAI
Jaroslaw Niebrzydowski, M.D. Medica Pro Familia ul. Chrzanowskiego 3/5 Gdynia, 81-338, Poland	Protocol SB2-G31-RA Site #SB21012 30 subjects randomized	October 10-14, 2016	NAI

Name of Sponsor, Address	Protocol # / Site # / # randomized	Inspection Date	Classification
Quintiles, Inc. Sponsor's U.S. Agent for Samsung Bioepis Co., Ltd. 4820 Emperor Blvd. Durham, NC 27703	Protocol SB2-G31-RA (Quintiles, Mumbai, India responsible for monitoring and data management)	August 2-5, 2016	NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data are unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Investigator

1. Nenad Prodanovic, M.D., Ph.D., Bosnia and Herzegovina

The inspection was conducted from September 5 to 9, 2016. A total of 36 subjects were screened, 31 subjects were enrolled and randomized. Thirty subjects completed the study. An audit of the 36 screened subjects' records enrolled at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was issued because the study was not conducted according to the investigational plan. Specifically:

(1) Ten subjects had portions of their scheduled visit assessment forms for efficacy endpoint subcomponent measures, specifically the Health Assessment Questionnaire (HAQ) and Subject Global Assessment (SGA) forms, completed or corrected by the Independent Joint Assessor (IJA), instead of the patient. Visit 1 (Baseline) HAQ and SGA forms were affected for nine of the ten subjects and most occurred at three of four visits. However, none of the affected forms were from the efficacy endpoint assessment visit (Visit 6, Week 30).

DCCE reviewer comment: Independent joint assessors were to be identified for each site, provided with standardized training, and kept distinct from other site staff in order to minimize biased assessments. The primary efficacy endpoint (ACR20 response) was determined by both improvement in physical parameters (i.e. ≥ 20 reduction from baseline in tender and swollen joints) and ≥ 20 reduction from baseline in three of five criteria (subject pain and subject global assessment, subject disability assessment, physician global assessment, and C-reactive protein [CRP]). For the primary efficacy endpoint determination, only Visit 1 (baseline) and Visit 6 assessments are of major relevance. Visit 1 was the most frequently observed visit (nine of ten subjects) that the Independent Joint Assessor potentially completed both joint and scale assessment and it occurred prior to randomization, so biased assessment based upon treatment assignment would not be anticipated, The IJA did not appear to be involved with the Visit 6 subcomponent scores and therefore, this violation is unlikely to have biased the efficacy determination at the study endpoint.

Involvement of the IJA with completion or correction of subcomponents of the efficacy endpoint at this site was discussed with the review division, DPARP. The Medical Team indicated that they have analytic procedures available to evaluate the contribution of each endpoint subcomponent to primary efficacy measure.

(2) Subjec (b) (6) was randomized to investigational drug product Kit Number (b) (6) at Visit 7 (Week 38) via IVRS, but was dispensed Kit Number (b) (6) instead.

DCCE reviewer comment: This observation was isolated in occurrence, and would not have an overall impact on the integrity of data.

(3) Drug dispensing records showed that five subjects received an incorrect calculated dosage of the investigational product.

DCCE reviewer Comment: These errors were considered rounding errors, within 0.5 milligram of the actual calculated dosage value, and were not considered significant.

Although regulatory violations were observed at the site, the data submitted by this clinical site appears to be acceptable in support of this specific indication.

2. **Jaroslaw Niebrzydowski, M.D.,** Gdynia, Poland

The inspection was conducted from October 10 to 14, 2016. A total of 36 subjects were screened, 30 enrolled and randomized, and 23 study subjects completed the study. An audit of the 30 randomized subjects' records enrolled at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection. No Form FDA 483 was issued.

The data submitted by this clinical site appears to be acceptable in support of this specific indication.

Sponsor

3. **Quintiles, Inc., Durham, NC** (Samsung Bioepis Co.,Ltd., US Agent, also Quintiles, Mumbai, India, responsible for study monitoring and data management)

This inspection was conducted from August 2 to 5, 2016 in North Carolina.

Quintiles (Contract Research Organization) records reviewed included the following: regulatory site set up, financial disclosures, site management and monitoring, electronic Trial Master File (eTMF) functional services, and Clinical Trial Management System (CTMS).

Monitoring visits including study site closeout were reviewed; monitoring reports indicated that the sites received adequate periodic monitoring. IRB approvals, site study protocol deviations, serious adverse events and related monitoring reports were assessed, and the CRO oversight appeared to be adequate. Quintiles (CRO) was responsible for the management of the electronic Trial Master File (eTMF) and no deviations were noted. Quintiles' standard operating procedure (SOP) index likewise revealed document identification, title, revision, document status, scope, effective date, and periodic review dates.

Records reviewed indicated that the CRO maintained adequate oversight of the clinical trial and monitoring activities were appropriate.

European Medicines Agency (EMA) audits

(b) (4)

(b) (4)

{See appended electronic signature page}

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Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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{See appended electronic signature page}

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Susan D. Thompson, M.D.
Team Leader and Acting Branch Chief,
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For: Kassa Ayalew, M.D., M.P.H.
Branch Chief, Good Clinical Practice Assessment Branch
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CC: Central Doc. Rm.
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DPARP/Associate Division Director/Sarah OkadaYim
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DPARP/Project Manager/ Christine Ford, MS, RPh
OSI/Office Director/David Burrow (Acting)
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OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Janice Pohlman/Susan D. Thompson
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/s/

ANTHONY J ORENCIA
12/09/2016

JANICE K POHLMAN
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SUSAN D THOMPSON
12/09/2016

M E M O R A N D U M

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

DATE: September 1, 2016

TO: Badrul Chowdhury, M.D., Ph.D.
Director, Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs

FROM: Kara A. Scheibner, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

Michael F. Skelly, Ph.D.
Lead Pharmacologist
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

Himanshu Gupta, Ph.D.
Staff Fellow
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director,
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Analytical inspection at (b) (4) covering BLA 761054, SB2, a proposed Biosimilar to Remicade (infliximab)

Inspection Summary:

At the request of the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) in the Office of New Drugs (OND), the Office of Study Integrity and Surveillance (OSIS) conducted

an inspection of the bioanalytical portions of study SB2-G11-NHV at [redacted]. Based upon the results of this inspection, we recommend that bioanalytical data in study SB2-G11-NHV be accepted for Agency review, but with several considerations and exceptions. See the Recommendation section below for details.

Study Audited during this Inspection:

Study Number: SB2-G11-NHV (BLA 761054)
Study Title: "A Randomized, Single-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics, Safety, Tolerability, and Immunogenicity of Three Formulations of Infliximab (SB2, EU Sourced Remicade® and US Sourced Remicade®) in Healthy Subjects"
Study Dates: July 13, 2013 through October 14, 2013
Number of Subjects Enrolled: 159
Sample Analysis: PK analysis: [redacted]
ADA analysis: [redacted]
NAb analysis: [redacted]

OSIS scientists Kara A. Scheibner, Ph.D., Michael F. Skelly, Ph.D., and Himanshu Gupta, Ph.D. conducted the inspection of bioanalytical portions of study SB2-G11-NHV from [redacted]

The bioanalytical audit included a thorough review of facilities and equipment, training records, current bioanalytical SOPs, study records and correspondence, method validation records, and interviews and discussions with [redacted] management and staff. Because of time constraints, no additional studies were selected for a surveillance assessment of the site. However, a bioequivalence inspection at [redacted] in [redacted] included a surveillance assessment.

At the conclusion of the inspection, a three-item Form FDA-483 was issued at [redacted] (**Attachment 1**). Additional minor observations were discussed throughout the week, and at the closing meeting. We received a formal response to the FDA-483 observations from [redacted] on [redacted] (**Attachment 2**). The FDA-483 observations, [redacted] response, and our evaluation of the observations and responses follow.

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Recommendation:

Following our examination of analytical data for study SB2-G11-NHV, observations made during the inspection and on Form FDA 483, and the responses received from (b) (4) we make the following recommendations:

Pharmacokinetic data: Data from the PK method validation and study sample analysis were found to be reliable. Therefore, we recommend that data from the PK portion of this study be accepted for further Agency review.

Anti-drug antibody data: Data for ADA are acceptable for further Agency review. The ADA screening assay was less sensitive than some diagnostic kits. However, the inappropriate false positive rate of 0.1% in the confirmatory assay caused seven study samples to be reported as confirmed negative; these additional seven samples should be considered as confirmed ADA-positive. Reviewers should assess ADA data with inclusion of these seven samples (b) (4)

Furthermore, the 12 study samples designated as inconclusive using the 99.9% CI cut point (b) (4)]) should be considered as ADA-positive.

Specificity and interference in the confirmatory assay were not fully validated. Reviewers should consider possible interferences by endogenous matrix components, hemolysis, and lipemia with reliability of the confirmatory assay.

Neutralizing antibody data: Data are acceptable for further Agency review. However, study samples with signal to noise ratios within 10% of the assay cut point may not be reliable because of high LPC concentration. This may have caused underestimation of NAb positive samples. In addition, the seven samples confirmed negative using the 99.9% CI cut point, but positive using the 99% CI cut point, may also have been NAb positive if they had been tested.

Kara A. Scheibner, Ph.D.
DGDBE, OSIS

Michael F. Skelly, Ph.D.
DGDBE, OSIS

Himanshu Gupta, Ph.D.
DGDBE, OSIS

Final Classification:

VAI: (b) (4) **(Analytical)**
(FEI#: (b) (4) **)**

CC:
OTS/OSIS/Kassim/Taylor/Haidar/Fenty-Stewart/Nkah/Miller/Kadavil
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala
OTS/OSIS/DGDBE/Cho/Skelly/Choi/Au/Scheibner/Gupta
Draft: KAS 8/10/2016, 8/30/2016
Edit: MFS 8/11/2016/2016, 8/30/2016; HG 8/12/2016/2016; JC 8/30/2016
OSIS file #: (b) (4)
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Bioanalytical Sites/ (b) (4)
FACTS: (b) (4)

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/s/

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09/01/2016

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M E M O R A N D U M

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

DATE: 8/12/2016

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

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

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: BLA 761054

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	PAREXEL International GmbH	Klinikum Westend, Spandauer Damm 130, 14050, Berlin, Germany

Reference ID: 3971881
Reference ID: 4152986

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/s/

SHILA S NKAH
08/12/2016